

*#10089215
09/22/04*

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/505, C07D 239/36	A1	(11) International Publication Number: WO 97/42956 (43) International Publication Date: 20 November 1997 (20.11.97)
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(21) International Application Number: PCT/US97/08335	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 16 May 1997 (16.05.97)	
(30) Priority Data: 08/648,768 16 May 1996 (16.05.96) US 60/017,801 16 May 1996 (16.05.96) US	
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(54) Title: DIDHYDROPYRIMIDINES AND USES THEREOF

(57) Abstract

This invention is directed to dihydropyrimidine compounds which are selective antagonists for human α_{1A} receptors. This invention is also related to uses of these compounds for lowering intraocular pressure, inhibiting cholesterol synthesis, relaxing lower urinary tract tissue, the treatment of benign prostatic hyperplasia, impotency, cardiac arrhythmia and for the treatment of any disease where the antagonism of the α_{1A} receptor may be useful. The invention further provides a pharmaceutical composition comprising a therapeutically effective amount of the above-defined compounds and a pharmaceutically acceptable carrier.

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Dihydropyrimidines and Uses Thereof

5 Throughout this application, various references are referred to within parentheses. Disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this
10 invention pertains.

Background of the Invention

15 The designation " α_{1A} " is the appellation recently approved by the IUPHAR Nomenclature Committee for the previously designated " α_{1c} " cloned subtype as outlined in the 1995 Receptor and Ion Channel Nomenclature Supplement (Watson and Girdlestone, 1995). The designation α_{1A} is used throughout this application and the supporting tables and figures to refer to this receptor subtype. At the same time, the receptor formerly designated α_{1A} was renamed α_{1B} . The new nomenclature is used throughout this application. Stable cell lines expressing these receptors are
20 described herein; however, these cell lines were deposited with the American Type Culture Collection (ATCC) under the old nomenclature (*infra*).
25

30 Benign Prostatic Hyperplasia (BPH), also called Benign Prostatic Hypertrophy, is a progressive condition which is characterized by a nodular enlargement of prostatic tissue resulting in obstruction of the urethra. This results in increased frequency of urination, nocturia, a poor urine stream and hesitancy or delay in starting
35 the urine flow. Chronic consequences of BPH can

include hypertrophy of bladder smooth muscle, a decompensated bladder and an increased incidence of urinary tract infection. The specific biochemical, histological and pharmacological properties of the prostate adenoma leading to the bladder outlet obstruction are not yet known. However, the development of BPH is considered to be an inescapable phenomenon for the aging male population. BPH is observed in approximately 70% of males over the age of 70. Currently, in the United States, the method of choice for treating BPH is surgery (Lepor, H., Urol. Clinics North Amer., 17, 651 (1990)). Over 400,000 prostatectomies are performed annually (data from 1986). A medicinal alternative to surgery is clearly very desirable. The limitations of surgery for treating BPH include the morbidity rate of an operative procedure in elderly men, persistence or recurrence of obstructive and irritative symptoms, as well as the significant cost of surgery.

α -Adrenergic receptors (McGrath, et. al. Med. Res. Rev., 9, 407-533, 1989) are specific neuroreceptor proteins located in the peripheral and central nervous systems on tissues and organs throughout the body. These receptors are important switches for controlling many physiological functions and, thus, represent important targets for drug development. In fact, many α -adrenergic drugs have been developed over the past 40 years. Examples include clonidine, phenoxybenzamine and prazosin (treatment of hypertension), naphazoline (nasal decongestant), and apraclonidine (treating glaucoma). α -Adrenergic drugs can be broken down into two distinct classes: agonists (clonidine and naphazoline are agonists), which mimic the receptor activation properties of the endogenous neurotransmitter norepinephrine, and antagonists (phenoxybenzamine and prazosin are antagonists), which act to block the effects of norepinephrine. Many of these drugs are effective but also produce unwanted

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side effects (for example, clonidine produces dry mouth and sedation in addition to its antihypertensive effects).

5 During the past 15 years a more precise understanding of α -adrenergic receptors and their drugs has evolved through increased scientific scrutiny. Prior to 1977, only one α -adrenergic receptor was known to exist. Between 1977 and 1988, it was accepted by the
10 scientific community that at least two α -adrenergic receptors-- α_1 and α_2 --existed in the central and peripheral nervous systems. Since 1988, new techniques in molecular biology have led to the identification of at least six α -adrenergic receptors which exist
15 throughout the central and peripheral nervous systems: α_{1A} (new nomenclature), α_{1B} , α_{1D} (new nomenclature), α_{2A} , α_{2B} and α_{2C} (Bylund, D.B., FASEB J., 6, 832 (1992)). In many cases, it is not known precisely which physiological responses in the body are controlled by
20 each of these receptors. In addition, current α -adrenergic drugs are not selective for any particular α -adrenergic receptor. Many of these drugs produce untoward side effects which may be attributed to their poor α -adrenergic receptor selectivity.

25 Since the mid 1970's, nonselective α -antagonists have been prescribed to treat BPH. In 1976, M. Caine, et al. (Brit. J. Urol., 48, 255 (1976)), reported that the nonselective α -antagonist phenoxybenzamine was useful in relieving the symptoms of BPH. This drug may produce its effects by interacting with α -receptors located on the prostate. However, this drug also produces significant side effects such as dizziness and asthenia which severely limit its use in treating
30 patients on a chronic basis. More recently, the α -adrenergic antagonists prazosin and terazosin have
35 also been found to be useful for treating BPH.

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However, these drugs also produce untoward side effects. It has recently been discovered that the α_{1A} receptor is responsible for mediating the contraction of human prostate smooth muscle (Gluchowski, C. et. al., WO 94/10989, 1994; Forray, C. et. al., Mol. Pharmacol. 45, 703, 1994). This discovery indicates that the α_{1A} antagonists may be effective agents for the treatment of BPH with decreased side effects. Further studies have indicated that the α_{1A} receptor may also be present in other lower urinary tract tissues, such as urethral smooth muscle (Ford et al. Br. J. Pharmacol., 114, 24P, (1995)).

This invention is directed to dihydropyrimidine compounds which are selective antagonists for cloned human α_{1A} receptors. This invention is also related to uses of these compounds for lowering intraocular pressure (Zhan, et. al. Ophthalmol. Vis. Sci., 34 Abst. #1133, 928, 1993), inhibiting cholesterol synthesis (D'Eletto and Javitt, J. Cardiovascular Pharmacol., 13 (Suppl. 2) S1-S4, 1989), benign prostatic hyperplasia, impotency (Milne and Wyllie, EP 0 459 666 A2, 1991), sympathetically mediated pain (Campbell, WO 92/14453, 1992), cardiac arrhythmia (Spiers, et. al., J. Cardiovascular Pharmacol., 16, 824-830, 1990) and for the treatment of any disease where antagonism of the α_{1A} receptor may be useful.

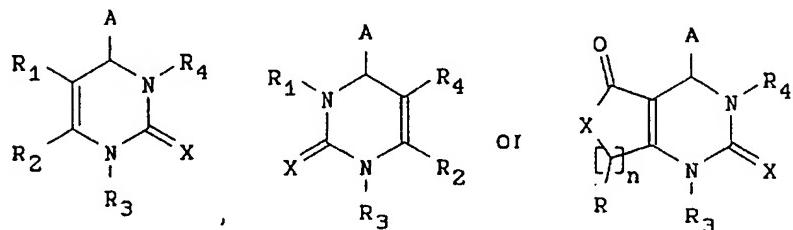
Summary of the Invention

This invention is directed to dihydropyrimidine compounds which are selective antagonists for human α_{1A} receptors. This invention is also related to uses of these compounds for lowering intraocular pressure, inhibiting cholesterol synthesis, relaxing lower urinary tract tissue, the treatment of benign prostatic hyperplasia, impotency, cardiac arrhythmia and for the treatment of any disease where antagonism of the α_{1A} receptor may be useful. The invention further provides a pharmaceutical composition comprising a therapeutically effective amount of the above-defined compounds and a pharmaceutically acceptable carrier.

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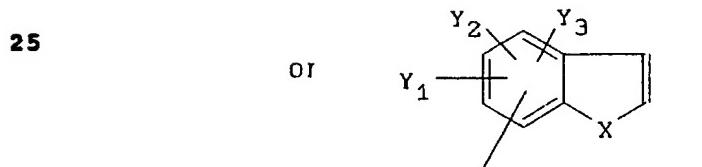
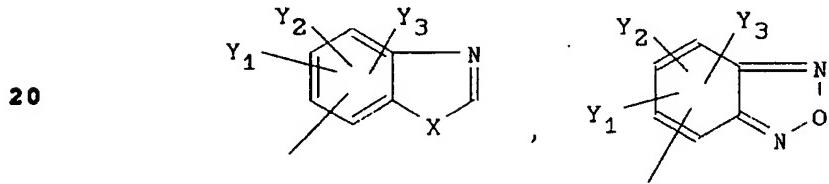
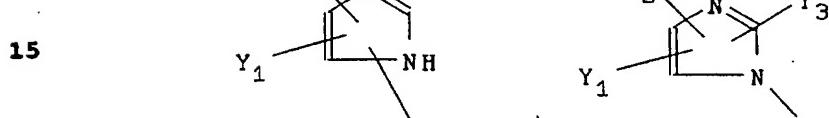
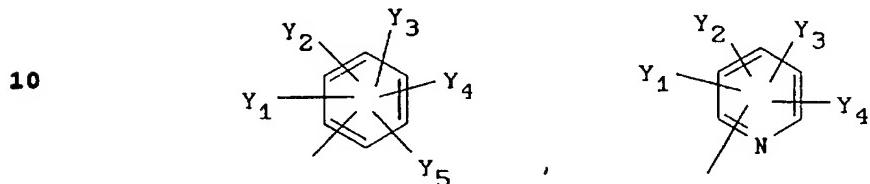
Detailed Description of the Invention

The present invention is directed to compounds having the structure:



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wherein A is



30

wherein each of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 is independently -H; straight chained or branched C_1 -C, alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 -C, alkenyl or alkynyl; C_3 -C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₃, -OCOR₃, -COR₃, -CONHR₃, -CON(R₃)₂, or -COOR₃; or any two of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 present on adjacent carbon atoms can 10 constitute a methylenedioxy group;

wherein X is S; O; or NR₃;

wherein R₁ is -H; -NO₂; -CN; straight chained or 15 branched C_1 -C, alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 -C, alkenyl or alkynyl; C_3 -C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂;

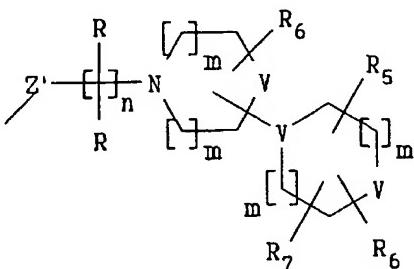
wherein R₂ is -H; straight chained or branched 25 C_1 -C, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 -C, alkenyl or alkynyl; C_3 -C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C_3 -C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃, - (CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃, or -CH₂X(CH₂)_pNHCXR₃; or -OR₃;

wherein each p is independently an integer from 1 35 to 7; wherein each n is independently an integer from 0 to 5;

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wherein each R₃ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein R_4 is



wherein Z' is $(CH_2)_n$, CO, $(CH_2)_nCO$, or $CO(CH_2)_n$;

wherein each V is independently O; S; CH_2 ; CR_5R_7 ;
C(R_7)₂; or NR₇;

wherein each m is independently an integer from 0 to 3; wherein σ is an integer from 1 to 3;

wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; or -OR₃;

30

wherein R₅ and R₇ each independently may be -H; F; Cl; Br; I; -COR₃; -CO₂R₃; -CON(R₃)₂; -CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; -(CH₂)_pOR₃; -(CH₂)_pSR₃; straight chained or branched C₁-C₇ alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl; wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more

35

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aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with -F, -Cl, -Br, -I, -NO₂, -CN, -OR₃, -SR₃, C₁-C₃ alkyl, or carboxamido; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more -F, -Cl, -Br,
5 -I, COR₃, CO₂R₃, -CON(R₃)₂, -CN, -NO₂, -N(R₃)₂, -OR₃, -SR₃, (CH₂)_nOR₃, (CH₂)_nSR₃; straight chained or branched C₁-C₃ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₃ alkenyl, C₂-C₃ alkynyl, C₃-C₅ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
10 cycloalkenyl; and

wherein each R₆ is independently -H; straight chained or branched C₁-C₃ alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₃ alkenyl or alkynyl; C₃-C₅ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
20 cycloalkenyl; or -OR₃;

or a pharmaceutically acceptable salt thereof.

The invention further provides for the (+) enantiomer
25 of any of the compounds described herein which is a cis isomer or a trans isomer. The invention also provides for the (-) enantiomer of any of the compounds described herein which is a cis or a trans isomer.

30 The compounds of the present invention are preferably at least 80% pure, more preferably 90% pure, and most preferably 95% pure.

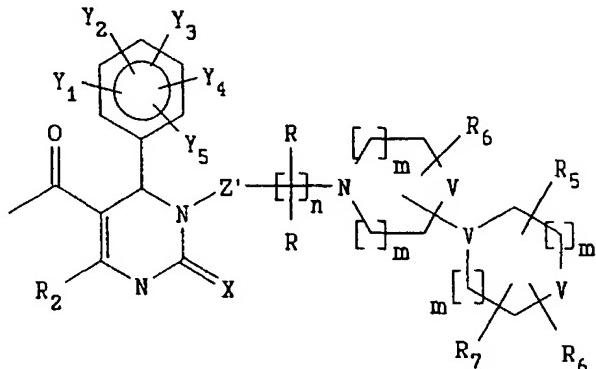
35 Ten fold selectivity differences are a minimum, but one skilled in the art will appreciate that compounds can be found that collectively have almost infinitely variable selective profiles. Compounds collectively having all possible combinations of selectivities are intended within the scope of this invention, provided

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that each of these compounds has at least ten-fold greater affinity for the α_{1A} receptor over the α_{1B} and/or α_{1D} receptors.

- 5 In one embodiment of the present invention the compound has the structure:

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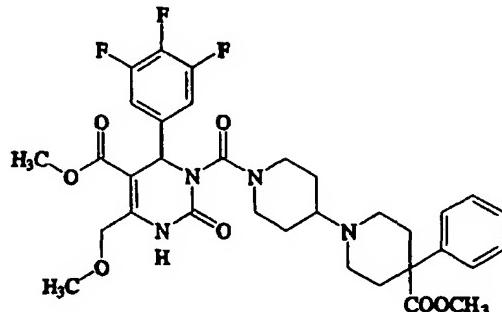
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In one embodiment of the present invention Z' is CO and n is 0.

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In another embodiment of the present invention the compounds have the structure:

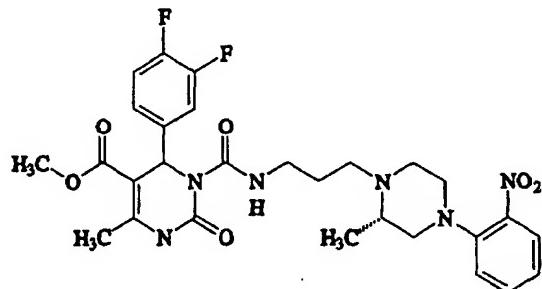
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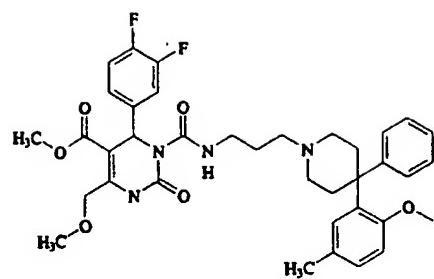
The invention provides for compounds having the following structures:

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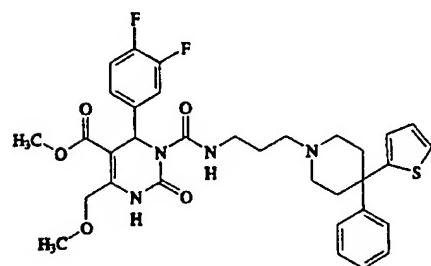
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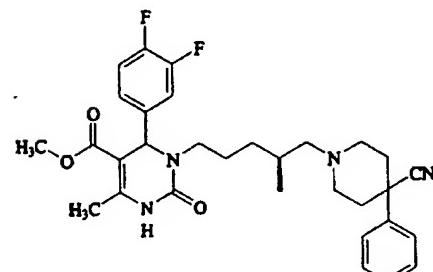
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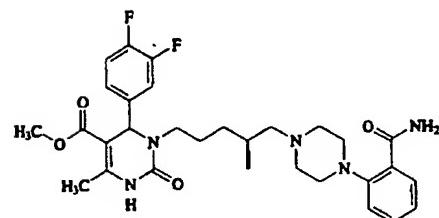
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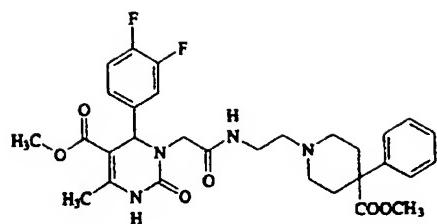
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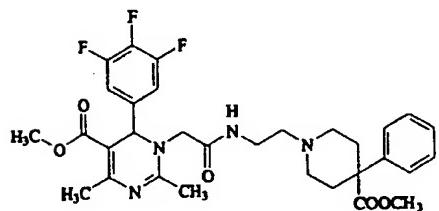
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and

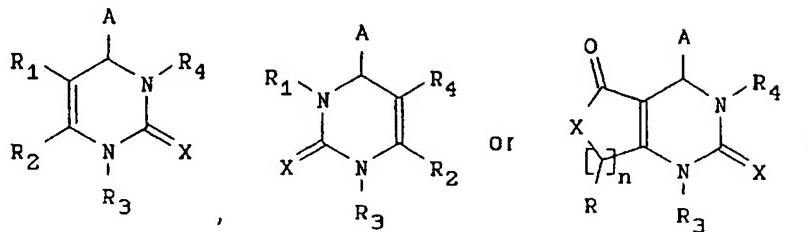
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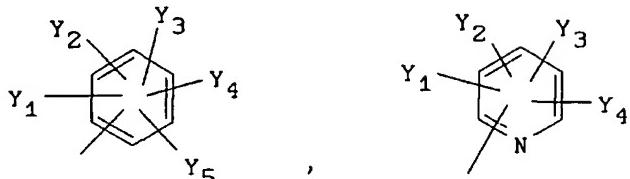
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The present invention is also directed to compounds having the structure:

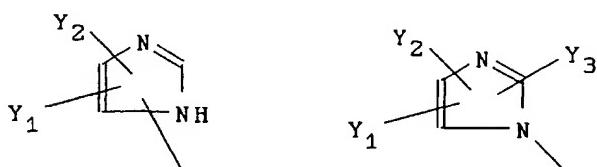


wherein A is

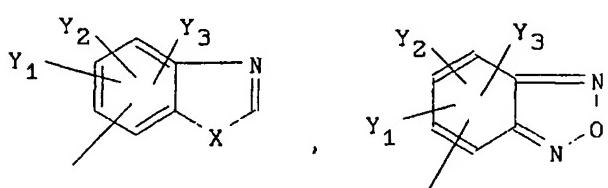
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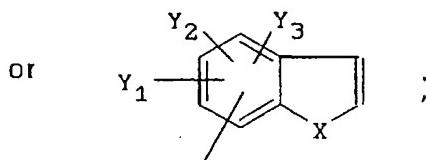
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25

wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,

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polyfluorocycloalkyl or cycloalkenyl; -F, -Cl,
-Br, or -I; -NO₂; -N₃; -CN; -OR₃, -OCOR₃, -COR₃,
-CONHR₃, -CON(R₃)₂, or -COOR₃; or any two of Y₁, Y₂,
Y₃, Y₄ and Y₅ present on adjacent carbon atoms can
5 constitute a methylenedioxy group;

wherein X is S; O; or NR₃;

10 wherein R₁ is -H; -NO₂; -CN; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -
15 CO₂R₃; or -CON(R₃)₂;

20 wherein R₂ is -H; straight chained or branched
C₁-C₇ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl,
monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₁₀
cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀
cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-
monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-
25 polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃,
-(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃, or
-CH₂X(CH₂)_pNHCXR₃; or -OR₃;

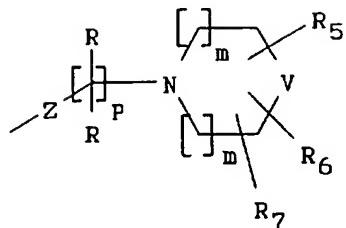
30 wherein each p is independently an integer from 1
to 7; wherein each n is independently an integer
from 0 to 5;

35 wherein each R₃ is independently -H; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

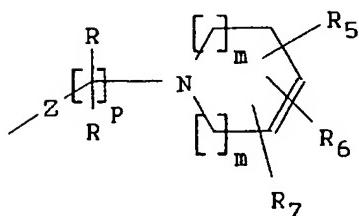
-15-

wherein R₄ is

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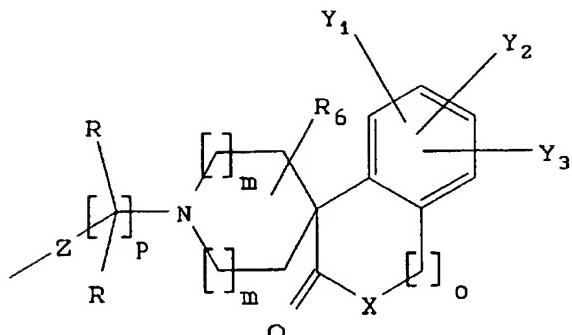


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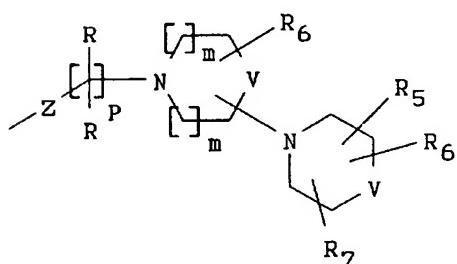
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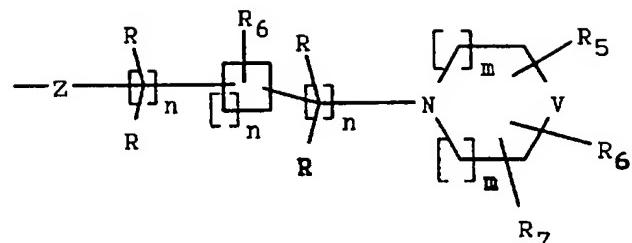
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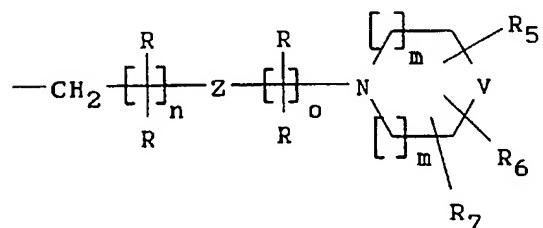
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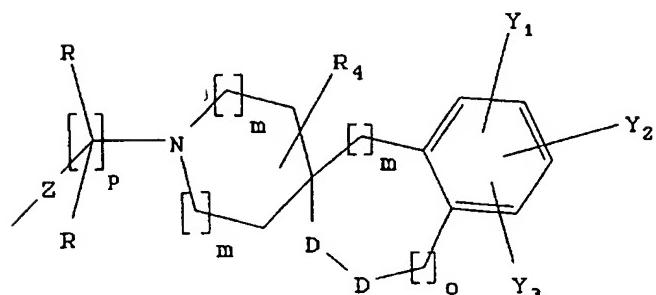
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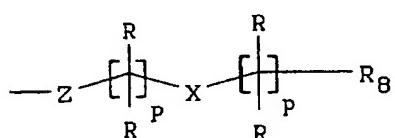


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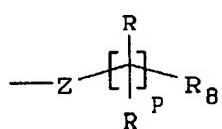
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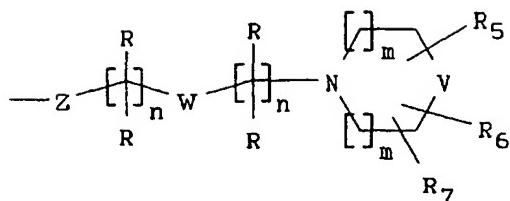
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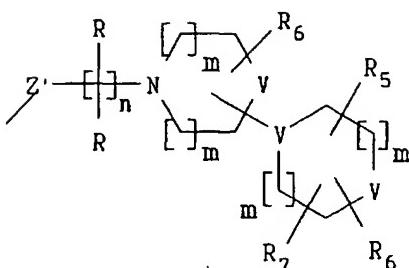


-17-



or

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wherein Z is C₂-C₇ alkenyl or alkynyl; CH₂; O; CO; CO₂; CONR₃; S; SO; SO₂; or NR₃;

20

wherein Z' is (CH₂)₀, CO, (CH₂)₀CO, or CO(CH₂)₀;

wherein each D is independently CH₂; O; S; NR₃; CO; or CS;

25

wherein W is C=O; C=NOR₃; substituted or unsubstituted phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl, wherein the phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl is substituted with -H, -F, -Cl, -Br, -I, -NO₂, -CN, straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇,

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alkynyl, C₃-C, cycloalkyl, C₃-C, monofluorocycloalkyl, C₃-C, polyfluorocycloalkyl, C₃-C, cycloalkenyl, -N(R₃)₂, -OR₃, -COR₃, -CO₂R₃, or -CON(R₃)₂;

5

wherein each V is independently O; S; CH₂; CR₅R₇; C(R₁)₂; or NR₇; provided that when V is CR₅R₇, the remaining carbons on the ring may only be substituted with R₆;

10

wherein each m is independently an integer from 0 to 3; wherein o is an integer from 1 to 3;

15

wherein each R is independently -H; -F; straight chained or branched C₁-C, alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C, alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; or -OR₃;

20

wherein R₅ is aryl or heteroaryl substituted with one or more of F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)₆OR₃; (CH₂)₆SR₃; straight chained or branched C₁-C, alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C, alkenyl, C₂-C, alkynyl, C₃-C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

25

30

wherein each R₆ is independently -H; straight chained or branched C₁-C, alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C, alkenyl or alkynyl; C₃-C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; or -OR₃;

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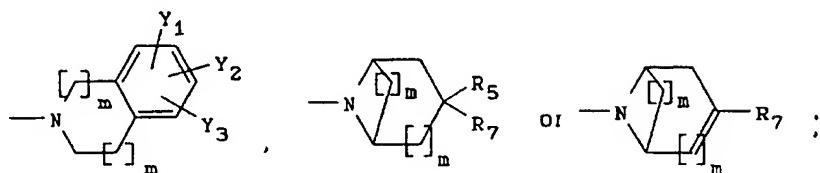
wherein R₁ is aryl or heteroaryl substituted with one or more of F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)₆OR₃; (CH₂)₆SR₃; straight chained or branched C₁-C, alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C, alkenyl, C₂-C, alkynyl, C₃-C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and

10

wherein R₂ is -H; substituted or unsubstituted benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolinyl, wherein the benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolinyl is substituted with -H, -F, -Cl, -Br, -I, -NO₂, -CN, straight chained or branched C₁-C, alkyl, straight chained or branched C₁-C, monofluoroalkyl, straight chained or branched C₂-C, alkenyl, straight chained or branched C₂-C, alkynyl, C₃-C, cycloalkyl, C₃-C, monofluorocycloalkyl, C₃-C, polyfluorocycloalkyl, C₃-C, cycloalkenyl, -N(R₃)₂, -OR₃, -COR₃, -CO₂R₃, or -CON(R₃)₂; substituted or unsubstituted straight chained or branched C₁-C, alkyl, monofluoroalkyl or polyfluoroalkyl; substituted or unsubstituted straight chained or branched C₂-C, alkenyl or alkynyl; C₃-C, cycloalkyl or cycloalkenyl, wherein the alkyl, monofluoroalkyl, polyfluoroalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl is substituted with -H, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl,

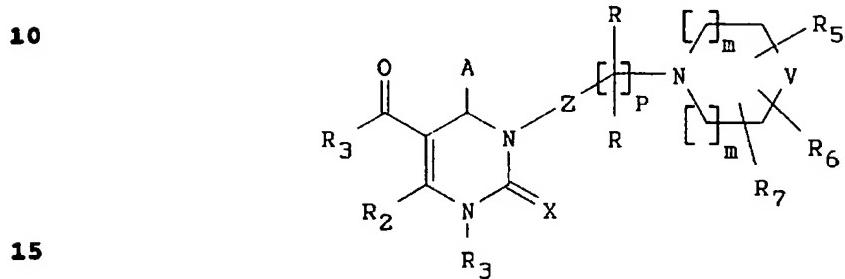
-20-

benzimidazolyl, $-N(R_3)_2$, $-NO_2$, $-CN$, $-CO_2R_3$, $-OR_3$;

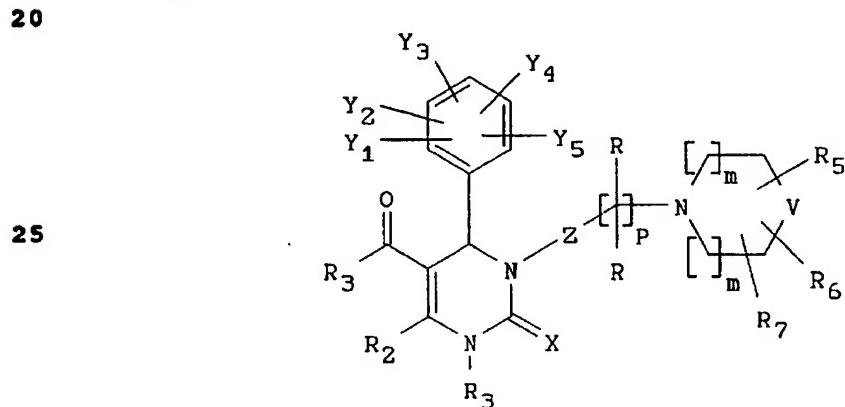


5 or a pharmaceutically acceptable salt thereof.

In one embodiment of the present invention the compounds have the following structure:



In a further embodiment of the present invention the compounds have the structure:



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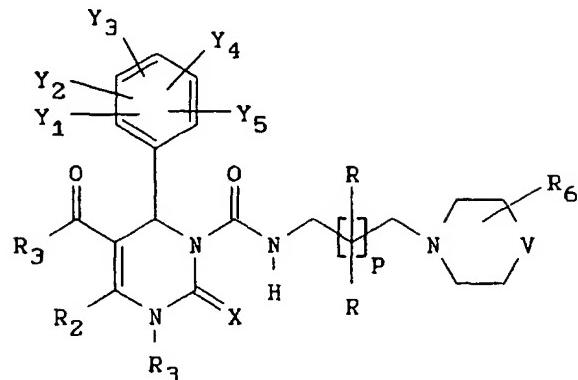
-21-

In one embodiment of the present invention the compounds have the structure:

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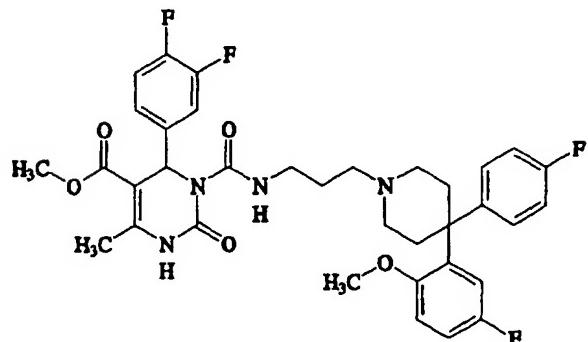
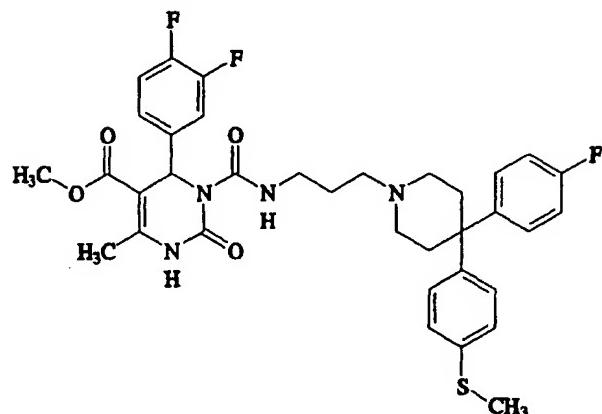
wherein V is selected from CR₅R₇ or NR₇, and p is selected from 1-3.

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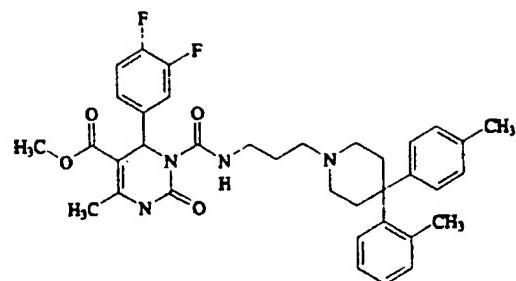
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and

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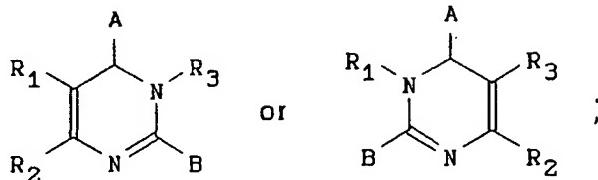


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The present invention is also directed to compounds having the structure:

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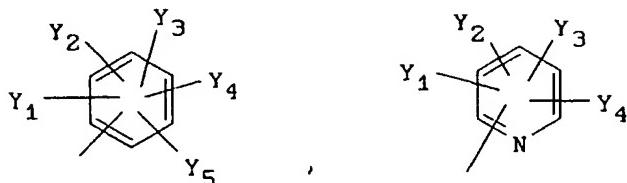


or

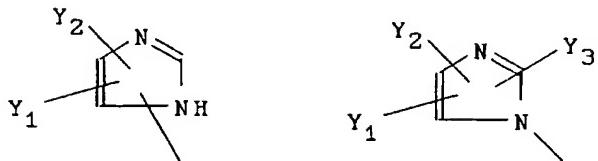
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wherein A is

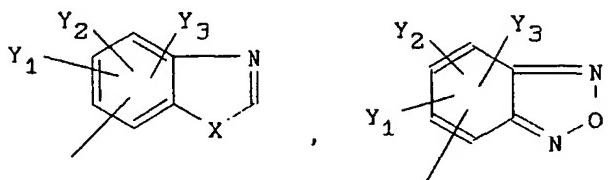
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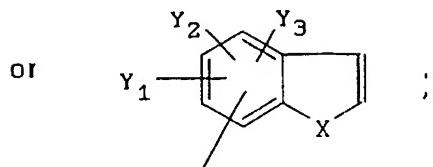
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wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,

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5 polyfluorocycloalkyl or cycloalkenyl; -F, -Cl,
-Br, or -I; -NO₂; -N₃; -CN; -OR₄, -OCOR₄, -COR₄,
-CONHR₄, -CON(R₄)₂, or -COOR₄; or any two of Y₁, Y₂,
Y₃, Y₄ and Y₅ present on adjacent carbon atoms can
constitute a methylenedioxy group;

wherein X is S; O; or NR₄;

10 wherein B is -H; straight chained or branched C₁-C,
alkyl, monofluoroalkyl, polyfluoroalkyl, alkoxy or
thioalkyl; straight chained or branched C₂-C,
alkenyl; -SCH₂C₆H₄OR₄; -(CH₂)_nC₆H₅; -CH₂X(CH₂)_nNHR₄;
-(CH₂)_nNHR₄; or -OR₄;

15 wherein R₁ is -H; -NO₂; -CN; straight chained or
branched C₁-C, alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C,
alkenyl or alkynyl; C₃-C, cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
20 cycloalkenyl; -N(R₄)₂; -OR₄; -(CH₂)_pOR₄; -COR₄; -
CO₂R₄; or -CON(R₄)₂;

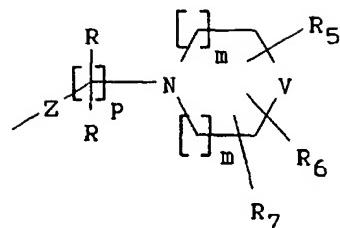
25 wherein R₂ is -H; straight chained or branched
C₁-C, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl,
monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C₂-C, alkenyl or alkynyl; C₃-C,
cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀
cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-
30 monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-
polyfluoroalkyl; -CN; -CH₂XR₄, -CH₂X(CH₂)_pNHR₄,
-(CH₂)_nNHR₄, -CH₂X(CH₂)_pN(R₄)₂, -CH₂X(CH₂)_pN₃, or
-CH₂X(CH₂)_pNHCXR₄; or -OR₄;

35 wherein each p is independently an integer from 1
to 7; wherein each n is independently an integer
from 0 to 5;

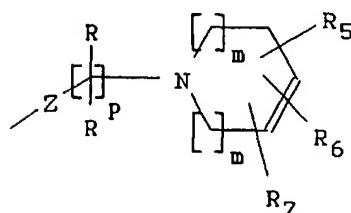
-25-

wherein R₃ is

5

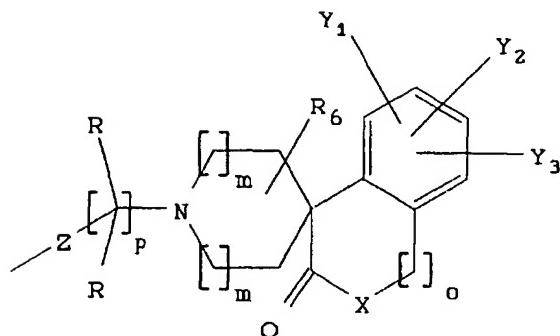


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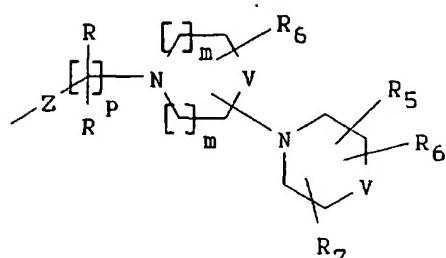
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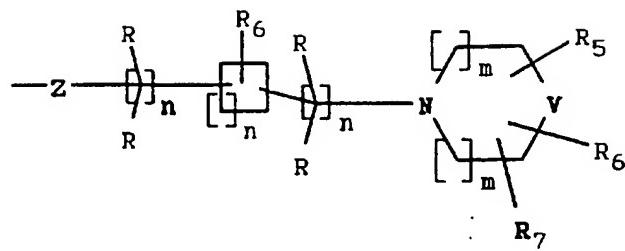
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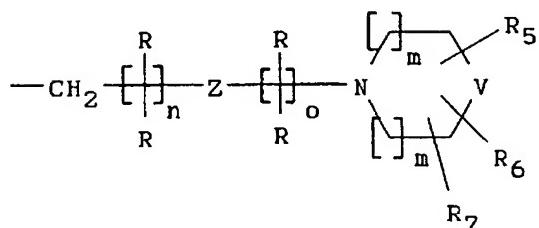
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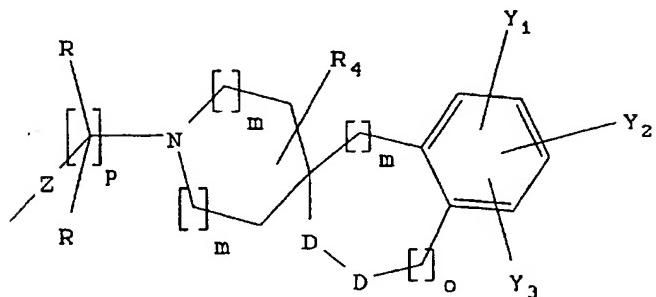


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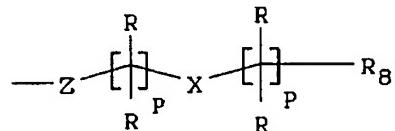


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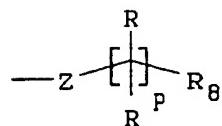
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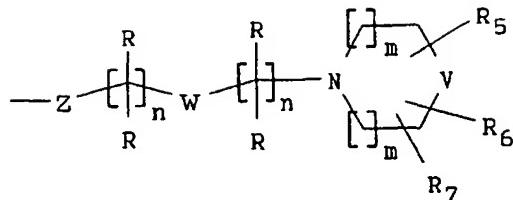
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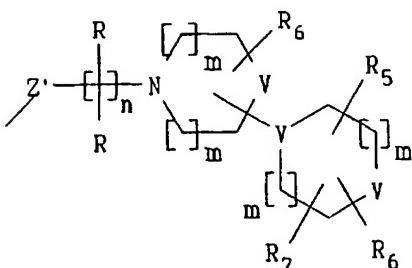
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or

10



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wherein Z is C₂-C₇ alkenyl or alkynyl; CH₂; O; CO;
CO₂; CONR₄; S; SO; SO₂; or NR₄;

20

wherein Z' is (CH₂)₀, CO, (CH₂)₀CO, or CO(CH₂)₀;

wherein each D is independently CH₂; O; S; NR₄; CO;
or CS;

25

wherein W is C=O; C=NOR₄; substituted or
unsubstituted phenyl, pyridyl, thiophenyl,
furanyl, pyrazinyl, pyrryl, naphthyl, indolyl,
imidazolyl, benzfurazanyl, benzfuranyl or
benzyimidazolyl, wherein the phenyl, pyridyl,
thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl,
indolyl, imidazolyl, benzfurazanyl, benzfuranyl or
benzyimidazolyl is substituted with -H, -F, -Cl, -
Br, -I, -NO₂, -CN, straight chained or branched
C₁-C₇ alkyl, straight chained or branched C₁-C₇
monofluoroalkyl, straight chained or branched C₁-C₇
polyfluoroalkyl, straight chained or branched C₂-C₇

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5 alkenyl, straight chained or branched C₂-C₇, alkynyl, C₃-C₇, cycloalkyl, C₃-C₇, monofluorocycloalkyl, C₃-C₇, polyfluorocycloalkyl, C₃-C₇, cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -CO₂R₄, or -CON(R₄)₂;

10 wherein each V is independently O; S; CH₂; CR₅R₇; C(R₇)₂; or NR₇; provided that when V is CR₅R₇ the remaining carbons on the ring may only be substituted with R₆;

15 wherein each m is independently an integer from 0 to 3; wherein o is an integer from 1 to 3;

20 15 wherein each R is independently -H; -F; straight chained or branched C₁-C₇, alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇, alkenyl or alkynyl; -N(R₄)₂; -NO₂; -CN; -CO₂R₄; or -OR₄;

25 20 wherein each R₄ is independently -H; straight chained or branched C₁-C₇, alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇, alkenyl or alkynyl; C₃-C₇, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

30 25 wherein R₅ is aryl or heteroaryl substituted with one or more of F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)₆OR₃; (CH₂)₆SR₃; straight chained or branched C₁-C₇, alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇, alkenyl, C₃-C₇, alkynyl, C₃-C₇, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

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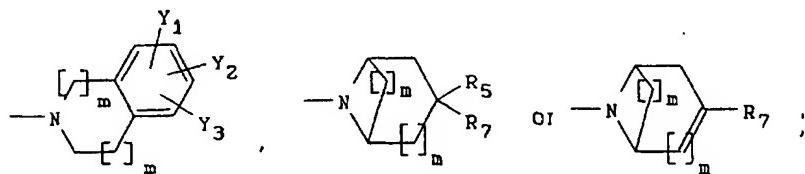
wherein each R₆ is independently -H; straight
chained or branched C₁-C₆ alkyl, hydroxyalkyl,
aminoalkyl, alkoxyalkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₆
5 alkenyl or alkynyl; C₃-C₆ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; or -OR₄;

wherein R₇ is aryl or heteroaryl substituted with
10 one or more of F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂;
CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)₆OR₃; (CH₂)₆SR₃;
straight chained or branched C₁-C₆ alkyl,
monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or branched
15 C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; and

wherein R₈ is -H; substituted or unsubstituted
20 benzyl, benzoyl, phenyl, pyridyl, thiophenyl,
furanyl, pyrazinyl, pyrryl, naphthyl, indolyl,
imidazolyl, benzfurazanyl, benzfuranyl,
benzimidazolyl or 2-keto-1-benzimidazolinyl,
wherein the benzyl, benzoyl, phenyl, pyridyl,
25 thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl,
indolyl, imidazolyl, benzfurazanyl, benzfuranyl,
benzimidazolyl or 2-keto-1-benzimidazolinyl is
substituted with -H, -F, -Cl, -Br, -I, -NO₂, -CN,
straight chained or branched C₁-C₆ alkyl, straight
30 chained or branched C₁-C₆ monofluoroalkyl, straight
chained or branched C₁-C₆ polyfluoroalkyl, straight
chained or branched C₂-C₆ alkenyl, straight chained
or branched C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆
monofluorocycloalkyl, C₃-C₆ polyfluorocycloalkyl,
35 C₃-C₆ cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -CO₂R₄, or
-CON(R₄)₂; substituted or unsubstituted straight
chained or branched C₁-C₆ alkyl, monofluoroalkyl or

-30-

polyfluoroalkyl; substituted or unsubstituted straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl or cycloalkenyl, wherein the alkyl, monofluoroalkyl, polyfluoroalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl is substituted with -H, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl, -N(R₄)₂, -NO₂, -CN, -CO₂R₄, -OR₄;

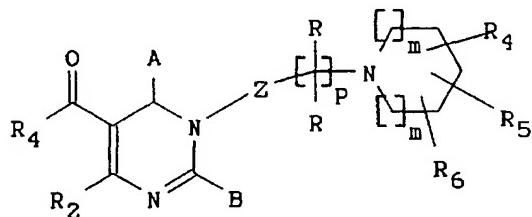


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or a pharmaceutically acceptable salt thereof.

In one embodiment of the present invention the
15 compounds have the following structure:

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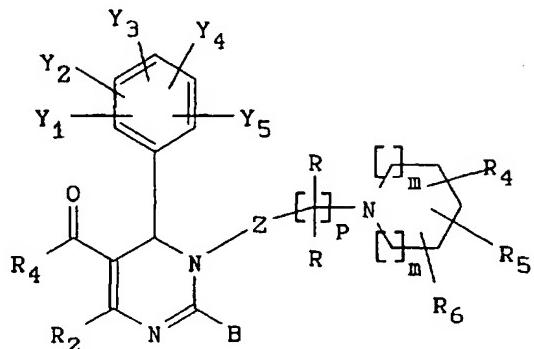


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In a further embodiment of the present invention the compounds have the structure:

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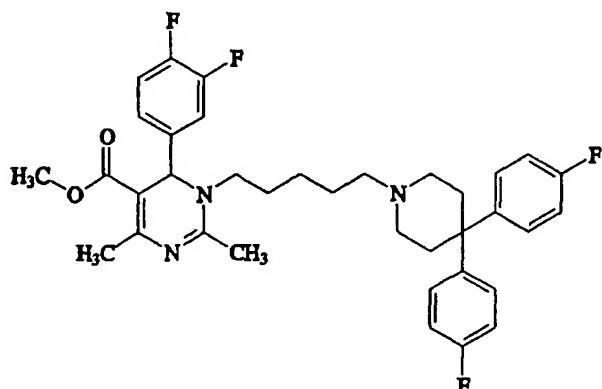
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The invention further provides for the embodiment having the following structures:

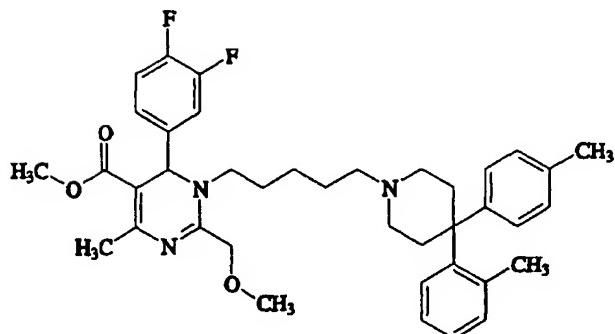
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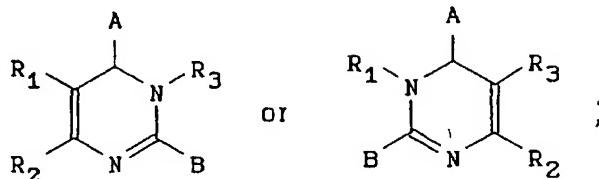
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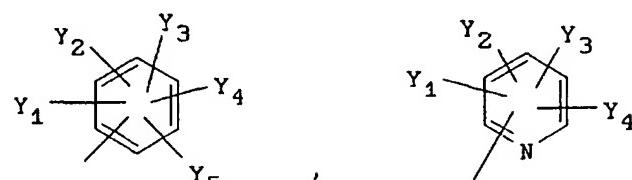
-32-

The present invention is also directed to compounds having the structure:

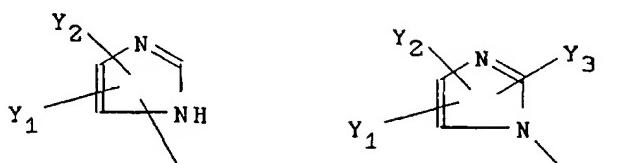
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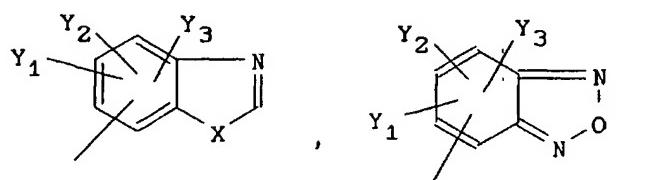
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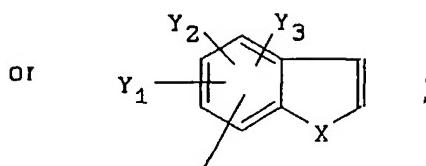
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wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₄, -OCOR₄, -COR₄,

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-CONHR₄, -CON(R₄)₂, or -COOR₄; or any two of Y₁, Y₂, Y₃, Y₄ and Y₅ present on adjacent carbon atoms can constitute a methylenedioxy group;

5 wherein X is S; O; or NR₄;

wherein B is -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, alkoxy or thioalkyl; straight chained or branched C₂-C₇ alkenyl; -SCH₂C₆H₄OR₄; -(CH₂)_nC₆H₅; -CH₂X(CH₂)_nNHR₄; -(CH₂)_nNHR₄; or -OR₄;

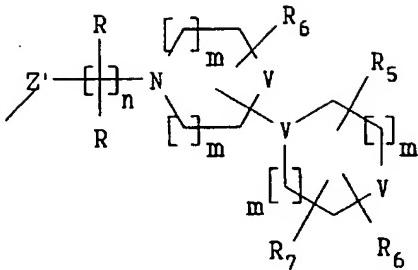
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15 wherein R₁ is -H; -NO₂; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₄)₂; -OR₄; -(CH₂)_pOR₄; -COR₄; -CO₂R₄; or -CON(R₄)₂;

20
25 wherein R₂ is -H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl or cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₄, -CH₂X(CH₂)_pNHR₄, -(CH₂)_nNHR₄, -CH₂X(CH₂)_pN(R₄)₂, -CH₂X(CH₂)_pN₃, or -CH₂X(CH₂)_pNHCXR₇; or -OR₄;

30
35 wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;

wherein R₃ is

5



10

wherein Z' is (CH₂)_o, CO, (CH₂)_oCO, or CO(CH₂)_o;

wherein each V is independently O; S; CH₂; CR₇R₇; C(R₇)₂; or NR₇;

15

wherein each m is independently an integer from 0 to 3; wherein o is an integer from 1 to 3;

20

wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₄)₂; -NO₂; -CN; -CO₂R₄; or -OR₄;

25

wherein each R₄ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

30

wherein R₅ and R₇ each independently may be -H; F; Cl; Br; I; -COR₃; -CO₂R₃; -CON(R₃)₂; -CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; -(CH₂)_pOR₃; -(CH₂)_pSR₃; straight chained or branched C₁-C₇ alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl; wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more

aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with -F, -Cl, -Br, -I, -NO₂, -CN, -OR₃, -SR₃, C₁-C₃ alkyl, or carboxamido; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more -F, -Cl, -Br,
5 -I, COR₃, -CON(R₃)₂, -CN, -NO₂, -N(R₃)₂, -OR₃, -SR₃, (CH₂)_nOR₃, (CH₂)_nSR₃; straight chained or branched C₁-C₃ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₃,
10 alkenyl, C₂-C₃ alkynyl, C₃-C₅ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and

15 wherein each R₆ is independently -H; straight chained or branched C₁-C₃ alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₃, alkenyl or alkynyl; C₃-C₅ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
20 cycloalkenyl; or -OR₄;

or a pharmaceutically acceptable salt thereof.

25 In the present invention aryl includes phenyl, benzyl, benzoyl or naphthyl and heteroaryl includes pyrazinyl, pyrryl, furanyl, thiophenyl, pyridyl, imidazolyl, indolyl, aminophenyl, benzamidyl, benzimidazolyl, benzfurazanyl, benzfuranyl, 2-keto-1-benzimidazolinyl or quinolyl.

30 The invention further provides for a pharmaceutical composition comprising a therapeutically effective amount of any of the compounds described above and a pharmaceutically acceptable carrier. In the subject invention a "therapeutically effective amount" is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes reduction, remission, or regression of the disease. In one embodiment the
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therapeutically effective amount is an amount from about 0.01 mg per subject per day to about 500 mg per subject per day, preferably from about 0.1 mg per subject per day to about 60 mg per subject per day and most preferably from about 1 mg per subject per day to about 20 mg per subject per day. In the practice of this invention the "pharmaceutically acceptable carrier" is any physiological carrier known to those of ordinary skill in the art useful in formulating pharmaceutical compositions.

In one preferred embodiment the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In another equally preferred embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream.

The invention provides a method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject any one of the compounds described herein effective to treat benign prostatic hyperplasia. In a preferred embodiment the compound of the pharmaceutical composition additionally does not cause a fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia. In one preferred embodiment the compound effects treatment of benign prostatic hyperplasia by relaxing lower urinary tract tissue and in particular where lower urinary tract tissue is prostatic smooth muscle.

The invention further provides a method of treating a subject suffering from elevated intraocular pressure which comprises administering to the subject one of the compounds described herein effective to lower intraocular pressure.

The invention further provides a method of treating a subject suffering from a disorder associated with elevated blood cholesterol which comprises administering to the subject one of the compounds described herein effective to inhibit cholesterol synthesis.

10 The invention also provides a method of treating a disease which is susceptible to treatment by antagonism of the α_{1A} receptor which comprises administering to the subject one of the compounds described herein effective to treat the disease.

15 The invention further provides a method of treating a subject suffering from impotency which comprises administering to the subject one of the compounds described herein effective to treat impotency.

20 The invention further provides a method of treating a subject suffering from sympathetically mediated pain which comprises administering to the subject one of the compounds described herein effective to treat sympathetically mediated pain.

25 The invention provides a method of treating a subject suffering from cardiac arrhythmia which comprises administering to the subject one of the compounds described herein effective to treat cardiac arrhythmia.

30 The invention provides a method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject one of the compounds described herein in combination with a 5 alpha-reductase inhibitor effective to treat benign prostatic hyperplasia. In one preferred embodiment the 5-alpha reductase inhibitor is finasteride. The dosage administered to the subject is about 0.01 mg per subject per day to 50 mg per subject per day of finasteride in combination with an α_{1A} antagonist. A

more preferred dosage administered to the subject is about 1 mg per subject per day to 7 mg per subject per day of finasteride in combination with an α_{1A} antagonist. The most preferred dosage administered to the subject is about 5 mg per subject per day of finasteride in combination with an α_{1A} antagonist.

The invention also provides for a pharmaceutical composition comprising a therapeutically effective amount of a combination of any of the compounds described herein in combination with finasteride and a pharmaceutically acceptable carrier. In one embodiment the pharmaceutical composition is a therapeutically effective amount of a combination comprising an amount from about 0.01 mg per subject per day to about 500 mg per subject per day of any one of the compounds described herein and an amount of finasteride of about 5 mg per subject per day. A more preferred embodiment of the pharmaceutical composition is a therapeutically effective amount of a combination comprising an amount from about 0.1 mg per subject per day to about 60 mg per subject per day of any one of the compounds described herein and an amount of the finasteride of about 5 mg per subject per day. The most preferred embodiment of the pharmaceutical composition is a therapeutically effective amount of a combination comprising from about 1 mg per subject per day to about 20 mg per subject per day of any one of the compounds described herein and an amount of finasteride of about 5 mg per subject per day.

The invention further provides a method of relaxing lower urinary tract tissue which comprises contacting the lower urinary tract tissue with an amount of one of the compounds described herein effective to relax lower urinary tract tissue. In one embodiment the lower urinary tract tissue is prostatic smooth muscle. In one preferred embodiment the compound additionally does not cause a fall in blood pressure when it is effective.

to relax lower urinary tract tissue.

The invention provides a method of relaxing lower urinary tract tissue in a subject which comprises 5 administering to the subject an amount of one of the compounds described herein effective to relax lower urinary tract tissue. In one preferred embodiment the compound does not cause a fall in blood pressure and the lower urinary tract tissue is prostatic smooth 10 muscle.

The invention further provides for a method of inhibiting contraction of prostatic tissue, which comprises administering to the subject an amount of any 15 of the compounds described herein effective to inhibit contraction of prostatic tissue. In one preferred embodiment the prostatic tissue is prostatic smooth muscle and the compound additionally does not cause a fall in blood pressure.

20 The invention provides for the use of the compounds described herein for the preparation of a pharmaceutical composition for lowering intraocular pressure, inhibiting cholesterol synthesis, and the treatment of: benign prostatic hyperplasia, impotency, 25 cardiac arrhythmia and any disease where antagonism of the α_{1A} receptor may be useful. The invention provides for the use of the compounds described herein for the preparation of a pharmaceutical composition for relaxing lower urinary tract tissue and in particular prostatic smooth muscle. The invention further provides for the use of any of compounds described 30 herein for the preparation of a pharmaceutical composition, where the compound additionally does not cause a fall in blood pressure at dosages effective to lower intraocular pressure, to inhibit cholesterol synthesis, and for the treatment of: benign prostatic 35 hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the α_{1A} receptor may be

useful.

The invention provides for the use of the compounds described herein in the preparation of a medicament for lowering intraocular pressure, inhibiting cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the α_{1A} receptor may be useful. The invention provides for the use of the compounds described herein in the preparation of a medicament for relaxing lower urinary tract tissue and in particular prostatic smooth muscle. The invention further provides for the use of any of compounds described herein in the preparation of a medicament, where the compound additionally does not cause a fall in blood pressure at dosages effective to lower intraocular pressure, to inhibit cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the α_{1A} receptor may be useful.

The invention provides for a drug which is useful for lowering intraocular pressure, inhibiting cholesterol synthesis, and the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the α_{1A} receptor may be useful, the effective ingredient of the said drug being any of the compounds described herein. The invention further provides the drug described herein additionally does not cause a fall in blood pressure at dosages effective to lower intraocular pressure, to inhibit cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the α_{1A} receptor may be useful.

The invention provides for a drug which is useful for relaxing lower urinary tract tissue and in particular prostatic smooth muscle, the effective ingredient of

the drug being any of the compounds described herein. The invention further provides the drug which is useful for relaxing lower urinary tract tissue additionally does not cause a fall in blood pressure at dosages effective to relax lower urinary tract tissue.

The invention also provides for the (-) and (+) enantiomers of all compounds of the subject application described herein. Included in this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The salts include but are not limited to the following acids and bases. The following inorganic acids; hydrochloric acid, hydrofluoric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and boric acid. The organic acids; acetic acid, trifluoroacetic acid, formic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid. The following inorganic bases; ammonia, hydroxyethylamine and hydrazine. The following organic bases; methylamine, ethylamine, propylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. This invention further provides for the hydrates and polymorphs of all of the compounds described herein.

In one preferred embodiment the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In another equally preferred embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream. In a further embodiment the compound may be formulated as a part of a pharmaceutically acceptable transdermal patch.

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A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl

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oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

- 5 Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, 10 intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or 15 other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings.
- 20 The compound can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents, for example, enough saline or glucose to make the solution isotonic, bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 25 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.
- 30 The compound can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, 35 and suspensions.

Optimal dosages to be administered may be determined by

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- those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.
- 10 One skilled in the art will readily appreciate that appropriate biological assays will be used to determine the therapeutic potential of the claimed compounds for the treating the above noted disorders.
- 15 This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully
20 in the claims which follow thereafter.

Experimental Details

For Examples 1-92 Scheme 1 describes the general synthetic preparation. All NMRs were obtained using a
5 300MHz GE QEPLUS NMR machine.

Example 1

1,6-Dihydro-5-methoxycarbonyl-2-[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-{N-[3-
10 (4,4-diphenylpiperidin-1-yl)propyl]}carboxamido
pyrimidine.

a. 4,4-Diphenylpiperidine hydrochloride. A mixture of
15 4-piperidone monohydrate hydrochloride (15.0 g, 0.0976 mol) and AlCl₃ (130 g, 0.976 mol, 10.0 eq) in anhydrous benzene (600 mL) were stirred at reflux for 4 hours. The mixture was cooled to room temperature, poured into ice (300 g) and water (50 mL), and filtered. The solid was washed with toluene and dried to afford 19.2 g
20 (72%) of an off-white solid, which was characterized spectroscopically.

b. 3-(4,4-Diphenylpiperidin-1-yl)propionitrile. To a suspension of 4,4-diphenylpiperidine hydrochloride (0.195 g, 0.712 mmol) in EtOH (1.5 mL) was added Et₃N (0.25 mL, 1.8 mmol, 2.6 eq) followed by acrylonitrile (0.13 mL, 2.01 mmol, 2.8 eq). The resulting solution was stirred at room temperature under argon for 15 min and then concentrated. Water was added, and the mixture was extracted with EtOAc (3 X 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated to give 170 mg (87%) of a tan solid, which was characterized spectroscopically and used in the next reaction without purification.
30

c. 3-(4,4-Diphenylpiperidin-1-yl)propylamine. To a stirred solution of 3-(4,4-diphenylpiperidin-1-

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yl)propionitrile (2.00 g, 6.89 mmol) in anhydrous THF (20 mL) under argon was added a solution of BH₃ in THF (1.0 M, 24.1 mL, 24 mmol, 3.5 eq) at room temperature. The mixture was refluxed for 4.5 hours and then cooled to room temperature. Aqueous HCl (6 N, 50 mL) was added and stirring was continued for 1 hour. The mixture was basified to pH 9 by addition of 6 N aq. NaOH, extracted with CH₂Cl₂ (3 X 10 mL), dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (SiO₂, EtOAc-MeOH-isopropylamine 9:1:0 to 4:1:0.2) to give 1.35 g (66%) of tan solid, which was characterized spectroscopically.

d. 2-(4-Methoxybenzyl)-2-thiopseudourea hydrochloride.

To a well-stirred suspension of thiourea (7.6 g, 0.1 mol) in THF (50 mL) at 0 °C, 4-methoxybenzyl chloride (16 g, 0.1 mol) was added in 10 min and the mixture was allowed to warm to room temperature. After 2 hours the mixture was heated to 65 °C and kept at that temperature for 5 hours. It was cooled to room temperature and diluted with diethyl ether (200 mL). The white precipitate formed was filtered and dried (22.5 g, 96%); m. p. 161-163 °C.

e. Methyl 2-{(4-nitrophenyl)methylene}-3-oxobutyrate. A mixture of 4-nitrobenzaldehyde (15.1 g, 0.1 mol), methyl acetoacetate (12.773 g, 0.11 mol), piperidine (0.41 g, 476 mL, 4.8 mmol), and acetic acid (0.288 g, 274 mL, 4.8 mmol) in 2-propanol (400 mL) was stirred at room temperature for 48 hours. The white solid, methyl 2-{(4-nitrophenyl)methylene}-3-oxobutyrate, formed was filtered, washed with 2-propanol (2 X 50 mL) and dried (21.80 g, 93%).

f. 1,6-Dihydro-5-methoxycarbonyl-2-[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)pyrimidine. A

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5 mixture of methyl 2-[(4-nitrophenyl)methylene]-3-oxobutyrate (8.96 g, 0.04 mol), 2-(4-methoxybenzyl)-2-thiopseudourea hydrochloride (9.28 g, 0.04 mol), and NaOAc (3.28 g, 0.04 mol) in DMF (100 mL) was stirred and heated at 70-75 °C for 4.5 hours. The mixture was cooled, poured into ice-water (300 mL), extracted with EtOAc (2 X 400 mL). The combined EtOAc extracts were washed with 10% NaHCO₃ solution (2 X 60 mL), brine (100 mL), and dried (MgSO₄). Solvent was evaporated and the crude product was purified by flash column chromatography on silica gel using 10% through 30% EtOAc in hexane as the gradient eluent, to leave the product as an oil, which on trituration with EtOAc/hexane became a yellow solid (11.4 g, 66.7%); m.p. 138-139 °C; ¹H-NMR (CDCl₃): δ 2.15 (s, 3 H), 3.62 (s, 3 H), 3.72 (s, 3 H), 4.05, 5.78 (s, d, J = 3 Hz, 1 H), 4.08, 4.20 (AB q, J = 12.5 Hz, 2 H), 4.21, 6.40 (s, d, J = 3 Hz, 1 H), 6.66 (2 d, J = 8.5 Hz, 2 H), 7.08 (2 d, J = 8.5 Hz, 2 H), 7.37 (2 d, J = 8.8 Hz, 2 H), 8.7 (2 d, J = 8.8 Hz, 2 H); Anal. Calcd. for C₂₁H₂₁N₃O₅S: C, 59.00; H, 4.95; N, 9.83. Found: C, 59.02; H, 4.93; N, 9.77.

25 g. 1,6-Dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.

To a well-stirred mixture of 1,6-dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)pyrimidine (4.5 g, 0.0105 mol), NaHCO₃ (3.69 g, 0.044 mol), CH₂Cl₂ (200 mL), and water (50 mL) at 0-5 °C, 4-nitrophenyl chloroformate (2.4 g, 0.0119 mol) was added in 5 min and the mixture was allowed to warm to room temperature. After 10 hours, the TLC analysis of the reaction mixture showed the presence of a small amount of starting pyrimidine, therefore, more 4-nitrophenyl chloroformate (0.65 g, 0.0032 mol) was added and the stirring continued for an additional 4

hours. The two layers were separated, the CH₂Cl₂ layer was washed with saturated aqueous NaHCO₃ solution (3 X 50 mL), dried (MgSO₄), and the solvent evaporated. The residue was recrystallized from CH₂Cl₂ and hexane to give the product as white crystals (5.5 g, 88.4%); m.p. 156-157 °C; ¹H-NMR (CDCl₃): δ 2.53 (s, 3 H), 3.70 (s, 3 H), 3.81 (s, 3 H), 4.06, 4.36 (AB q, J = 13.5 Hz, 2 H), 6.30 (s, 1 H), 6.78 (d, J = 8.7 Hz, 2 H), 7.17 (d, J = 8.5 Hz, 2 H), 7.20 (d, J = 8.7 Hz, 2 H), 7.32 (d, J = 8.8 Hz, 2 H), 7.97 (d, J = 8.8 Hz, 2 H), 8.25 (d, J = 8.8 Hz, 2 H); Anal. Calcd. for C₂₈H₂₄N₄O₃S: C, 56.75; H, 4.08; N, 9.45. Found: C, 56.49; H, 4.28; N, 9.25.

15 h. 1,6-Dihydro-5-methoxycarbonyl-2-[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4,4-diphenylpiperidin-1-yl)propyl]carboxamido}pyrimidine.

To a stirred solution of 1,6-dihydro-5-methoxycarbonyl-2-[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-{(4-nitrophenyloxy)carbonyl}pyrimidine (0.592 g, 1 mmol) in anhydrous THF (10 mL) at room temperature under argon atmosphere, a solution of 3-[4,4-diphenylpiperidin-1-yl]propylamine (0.441 g, 1.5 mmol, 1.5 eq) in THF (5 mL) was added and the stirring continued for 1 hours. Solvent was evaporated from the reaction mixture and the residue was redissolved in CH₂Cl₂ (50 mL), washed with 5% NaHCO₃ (3 X 25 mL), brine (50 mL), and dried (MgSO₄). Solvent was evaporated and the residue was purified by flash chromatography on silica gel using 10% methanol in EtOAc as the eluent to give the desired product as an oil, which on trituration with hexane and drops of EtOAc became a white powder (0.32 g, 43%); m.p. 79-80 °C; ¹H-NMR (CDCl₃): δ 1.61-1.82 (m, 4 H), 2.27 (s, 3 H), 2.30-2.51 (m, 8 H), 3.19-3.36 (m, 1 H), 3.42-3.60 (m, 1 H), 3.68 (s, 3 H), 3.76 (s, 3 H), 3.95, 4.22 (AB q, J = 13.6 Hz, 2 H), 6.16 (s, 1 H), 6.70 (d, J = 8.6 Hz, 2 H), 7.04

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(d, $J = 8.6$ Hz, 2 H), 7.11-7.29 (m, 12 H), 7.68 (br t, 1 H, NH), 7.91 (d, $J = 8.8$ Hz, 2 H); Anal. Calcd. for $C_{42}H_{45}N_5O_6S \cdot 0.33 CH_2Cl_2$: C, 65.52; H, 5.93; N, 9.03. Found: C, 65.52; H, 6.01; N, 9.20.

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Example 2

1,6-Dihydro-5-methoxycarbonyl-2-[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4-phenylpiperidin-1-yl)propyl]}carboxamidopyrimidine.

a. 3-(4-Phenylpiperidin-1-yl)propionitrile. Acrylonitrile (3.1 mL, 44 mmol, 2.5 eq) was added to a solution of 4-phenylpiperidine (3.0 g, 18 mmol) in EtOH (40 mL) and the mixture was stirred at room temperature for 1.5 hours. The volatiles were removed to give 3.8 g of pure product (brown oil, 99%), which was characterized spectroscopically.

b. 3-(4-Phenylpiperidin-1-yl)propylamine. To a stirred solution of 3-(4-phenylpiperidin-1-yl)propionitrile (5.1 g, 24 mmol) in anhydrous THF (20 mL) under argon was added a solution of BH_3 in THF (1.0 M, 83 mL, 83 mmol, 3.5 eq) at room temperature. The mixture was refluxed for 4.5 hours and then cooled to room temperature. Aqueous HCl (6 N, 130 mL) was added and stirring was continued for 2 hours at 50-70 °C. The mixture was basified to pH 9 by addition of 6 N aq. NaOH and extracted with EtOAc (100 mL) and CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and treated with HCl in ether (1.0 M, 50 mL). The solvents were removed, ether (250 mL) was added, the mixture was filtered, and the filter cake was washed with ether. Water (60 mL) was added to the resulting white solid, the pH was adjusted to 10-11 with 1 N NaOH, and the aqueous phase was extracted with

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CH_2Cl_2 (3 X 50 mL). The combined extracts were dried (MgSO_4) and the solvents evaporated to give 4.5 g (87%) of pure product (light brown solid), which was characterized spectroscopically.

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c. 1,6-Dihydro-5-methoxycarbonyl-2-[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4-phenylpiperidin-1-yl)propyl]carboxamido pyrimidine. This compound was prepared from 1,6-dihydro-5-methoxycarbonyl-2-[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.77 g, 1.3 mmol), 3-[4-phenylpiperidin-1-yl] propylamine (0.34 g, 1.56 mmol, 1.2 eq) and purified using similar conditions described in Example 1 (0.63 g, 72%); m.p. 123-124 °C; $^1\text{H-NMR}$ (CDCl_3): δ 1.65-2.10 (m, 8 H), 2.41 (s, 3 H), 2.41-2.55 (m, 3 H), 2.99-3.06 (m, 2 H), 3.2-3.35 (m, 1 H), 3.45-3.60 (m, 1 H), 3.67 (s, 3 H), 3.75 (s, 3 H), 4.10, 4.33 (AB q, J = 13.6 Hz, 2 H), 6.19 (s, 1 H), 6.71 (d, J = 8.6 Hz, 2 H), 7.09 (d, J = 8.6 Hz, 2 H), 7.20-7.34 (m, 7 H), 7.97 (br t, 1 H, NH), 7.97 (d, J = 8.8 Hz, 2 H); Anal. Calcd. for $\text{C}_{36}\text{H}_{41}\text{N}_5\text{O}_6\text{S}$.0.25 CH_2Cl_2 : C, 62.82; H, 6.04; N, 10.11. Found: C, 62.54; H, 6.13; N, 10.03.

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Example 3

1-{N-[3-(4-Cyano-4-phenylpiperidin-1-yl)propyl]} carboxamido-1,6-dihydro-5-methoxycarbonyl-2-[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl) pyrimidine.

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a. 3-(4-Cyano-4-phenylpiperidinyl)propylamine. 4-Cyano-4-phenylpiperidine hydrochloride (5.01 g, 22.5 mmol) was added to water (100 mL), and the solution was basified to pH 10-11 by addition of 6 N aqueous NaOH. The mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried (MgSO_4) and

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concentrated. To the residue were added 3-bromopropylamine hydrobromide (4.92 g, 22.5 mmol), anhydrous K₂CO₃ (3.42 g, 24.8 mmol, 1.10 eq), and 1,4-dioxane (100 mL). The mixture was stirred at reflux for 24 hours under a CaSO₄ drying tube. The solvent was evaporated, and the product was purified by flash chromatography (SiO₂, CHCl₃/MeOH/2 M NH₃ in MeOH (100:8:4 to 100:20:8) to give 3.23 g (59%) of colorless oil, which was characterized spectroscopically.

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b. 1-[N-[3-(4-Cyano-4-phenylpiperidin-1-yl)propyl] carboxamido-1,6-dihydro-5-methoxycarbonyl-2[{(4-methoxy-phenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)pyrimidine.

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This compound was prepared from 1,6-dihydro-5-methoxy carbonyl-2-{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.592 g, 1 mmol), 3-[4-cyano-4-phenyl piperidin-1-yl]propylamine (0.292 g, 1.2 mmol, 1.2 eq)

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and purified using similar conditions described in Example 1 (0.445 g, 64%); m.p. 143-144 °C; ¹H-NMR (CDCl₃): δ 1.70-1.86 (m, 2 H), 2.02-2.09 (m, 4 H), 2.38 (s, 3 H), 2.41-2.56 (m, 4 H), 2.95-3.02 (m, 2 H), 3.24-3.40 (m, 1 H), 3.42-3.58 (m, 1 H), 3.68 (s, 3 H), 3.76 (s, 3 H), 4.08, 4.23 (AB q, J = 13.5 Hz, 2 H), 6.23 (s, 1 H), 6.72 (d, J = 8.6 Hz, 2 H), 6.94 (br t, 1 H, NH), 7.08 (d, J = 8.6 Hz, 2 H), 7.29 (d, J = 8.7 Hz, 2 H), 7.33-7.49 (m, 5 H), 7.94 (d, J = 8.8 Hz, 2 H); Anal. Calcd. for C₃₇H₄₀N₆O₆S: C, 63.78; H, 5.79; N, 12.06.

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Found: C, 63.86; H, 5.90; N, 11.92.

Example 4

1,6-Dihydro-5-methoxycarbonyl-1-[N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl] carboxamido-2-{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)pyrimidine.

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a. 4-Methoxycarbonyl-4-phenylpiperidine. To a stirred solution of H₂SO₄ (16 mL) in MeOH (400 mL), 4-phenyl-4-piperidinecarboxylic acid 4-methyl benzenesulfonate (37.7 g, 0.1 mole) was added and the mixture was stirred and refluxed for 8 hours. Excess methanol was evaporated at reduced pressure and the residue was poured into a mixture of ice and 6 N NaOH. The pH was adjusted to 10-11 by adding more 6 N NaOH and extracted with CH₂Cl₂ (3 X 150 mL). The combined CH₂Cl₂ extracts were dried (MgSO₄) and the solvent evaporated to leave the desired product as a viscous oil. The product (20.2 g, 92%) was used without further purification.

b. 3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine.

A mixture of 4-methoxycarbonyl-4-phenylpiperidine (8.5 g, 0.039 mol), 3-bromopropylamine hydrobromide (12.7 g, 0.058 mol), potassium carbonate (13.475 g, 0.0957 mole), and KI (3.24 g, 0.0195 mol) in 1,4-dioxane (200 mL) was stirred and refluxed for 24 hours. Dioxane was evaporated at reduced pressure, the residue was treated with ice-cold 6 N NaOH (400 mL) and extracted with CH₂Cl₂ (4 X 120 mL). Solvent was evaporated from the combined dried (K₂CO₃) extracts and the residue was purified by column chromatography on silica gel using CHCl₃/MeOH/2 M NH₃, in MeOH (20:2:1) as the eluent to afford the product as a viscous oil (7.8 g, 72%).

c. 1,6-Dihydro-5-methoxycarbonyl-1-[N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)pyrimidine. This compound was prepared from 1,6-dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyl-oxy)carbonyl]pyrimidine (1.0 g, 1.69 mmol), 3-[4-methoxycarbonyl-4-phenyl

piperidin-1-yl}propylamine (0.56 g, 2.03 mmol, 1.2 eq) and purified using similar conditions described in Example 1 (1.085 g, 88%); m.p. 140-141 °C; ¹H-NMR (CDCl₃): δ 1.62-1.74 (m, 2 H), 1.82-2.18 (m, 4 H), 2.21 (s, 3 H), 2.35-2.58 (m, 4 H), 2.75-2.89 (m, 2 H), 3.18-3.30 (m, 1 H), 3.42-3.58 (m, 1 H), 3.61 (s, 3 H), 3.66 (s, 3 H), 3.75 (s, 3 H), 3.91, 4.15 (AB q, J = 13.6 Hz, 2 H), 6.14 (s, 1 H), 6.69 (d, J = 8.6 Hz, 2 H), 7.02 (d, J = 8.6 Hz, 2 H), 7.20-7.37 (m, 7 H), 7.56 (br t, 1 H, NH), 7.90 (d, J = 8.8 Hz, 2 H); Anal. Calcd. for C₃₈H₄₃N₅O₆S: C, 62.54; H, 5.94; N, 9.60. Found: C, 62.41; H, 6.06; N, 9.34.

Example 5

15 5-Methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4,4-diphenyl-piperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-thioxo-pyrimidine.

To a stirred solution of 1,6-dihydro-6-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4,4-diphenylpiperidin-1-yl)propyl]}carboxamidopyrimidine (0.14 g, 0.187 mmol) and ethanethiol (0.5 mL) in CH₂Cl₂ (5 mL) at 5 °C under argon, TFA (0.5 mL) was added and the mixture was allowed to warm to room temperature. After 3 hours, solvents were evaporated completely, the residue was redissolved in EtOAc (10 mL), washed with 5% NaHCO₃ (5 X 1 mL) and dried (MgSO₄). Solvent was evaporated and the residue was purified by column chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.096 g, 82%); m.p. 130-131 °C; ¹H-NMR (CDCl₃): δ 1.65-1.80 (m, 2 H), 2.31 (s, 3 H), 2.31-2.49 (m, 10 H), 3.25-3.55 (m, 2 H), 3.76 (s, 3 H), 7.01 (s, 1 H), 7.09-7.29 (m, 6 H), 7.41 (d, J = 8.2 Hz, 2 H), 8.11 (d, J = 8.8 Hz, 2 H), 9.76 (br t, 1 H, NH); Anal. Calcd. for C₃₄H₃₇N₅O₆S·0.3 H₂O: C, 64.50; H, 5.89; N, 11.06. Found: C, 64.45; H, 6.05; N, 10.87.

Example 6

1-[N-[3-(4-(4-Methoxyphenyl)-4-phenylpiperidin-1-yl)propyl]carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1,2,3,6-tetrahydro-2-thioxo
5 pyrimidine.

a. 4-(4-Methoxyphenyl)-4-phenylpiperidine. 4-Hydroxy-4-phenylpiperidine (5.00 g, 28.2 mmol) was added to a suspension of AlCl₃ (18.8 g, 0.141 mol, 5.00 eq) in anhydrous anisole (100 mL). The mixture was stirred at room temperature for 1 hours and then heated to 50 °C for 3.5 hours. It was cooled to room temperature and poured cautiously into ice-water. The mixture was basified to pH 11 by addition of 6 N aqueous NaOH, and extracted with EtOAc (3 x 75 mL). The combined organic extracts were applied directly to a flash chromatography column, which was eluted with CH₂Cl₂/0.67 M NH₃ in MeOH (4:1) to afford 1.683 g (22%) of light yellow oil, which was characterized spectroscopically.

b. 3-[4-(4-Methoxyphenyl)-4-phenylpiperidin-1-yl]propionitrile. Acrylonitrile (1.03 mL, 15.7 mmol, 2.50 eq) was added at 0 °C to a solution of 4-(4-methoxyphenyl)-4-phenylpiperidine (1.68 g, 6.28 mmol) in EtOH (20 mL) and the resulting solution was stirred for 1.5 hours at room temperature. After removal of the solvent, the residue was purified by flash chromatography (SiO₂, EtOAc-CHCl₃, 1:3) to give 1.41 g (70%) of colorless oil, which was characterized spectroscopically.

c. 3-[4-(4-Methoxyphenyl)-4-phenylpiperidin-1-yl]propylamine. To a stirred solution of 3-[4-(4-methoxyphenyl)-4-phenylpiperidin-1-yl]propionitrile (1.41 g, 4.40 mmol) in anhydrous THF (10 mL) under argon was added a solution of BH₃ in THF (1.0 M, 11.0 mL, 2.5 eq) at room temperature. The mixture was

refluxed for 4.5 hours and then cooled to room temperature. Aqueous HCl (6 N, 15 mL) was added and stirring was continued for 2 h at 55-60 °C. The mixture was basified to pH 9 by addition of 6 N aq. 5 NaOH and extracted with CH₂Cl₂ (3 x 75 mL). The combined organic solutions were dried (MgSO₄) and concentrated. The residue was dissolved in CH₂Cl₂ (10 mL) and treated with HCl in ether (1.0 M, 9.0 mL, 2.0 eq). The solvents were removed, ether (30 mL) was 10 added, the mixture was filtered, and the filter cake was washed with ether (2 x 10 mL). Water (20 mL) was added to the resulting white solid, the pH was adjusted to 10 with 1 N NaOH, and the aqueous phase was extracted with CH₂Cl₂ (3 x 40 mL). The combined organic 15 extracts were dried (MgSO₄) and concentrated to give 610 mg (43%) of white solid, which was characterized spectroscopically.

d. 1-{N-[3-(4-Methoxyphenyl)-4-phenylpiperidin-1-yl] 20 propyl}carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1,2,3,6-tetrahydro-2-thioxopyrimidine.

To a stirred mixture of 1,6-dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.592 g, 1 mmol) and K₂CO₃ (0.276 g, 2 mmol) in anhydrous THF (10 mL) at room temperature under argon atmosphere, a solution of 3-[4-(4-methoxyphenyl)-4-phenylpiperidin-1-yl]propylamine (0.390 g, 1.2 mmol, 1.2 eq) 25 in THF (10 mL) was added and the stirring was continued for 1 hour. Solvent was evaporated from the reaction mixture and the residue was redissolved in CH₂Cl₂ (50 mL), washed with 5% NaHCO₃ (3 X 25 mL), brine (50 mL), and dried (MgSO₄). The CH₂Cl₂ solution was filtered and 30 cooled to 5 °C. To this, ethanethiol (0.5 mL) and TFA (0.5 mL) were added and the mixture was stirred and allowed to warm to room temperature. After 3 hours,

solvents were evaporated completely, the residue was redissolved in EtOAc (10 mL), washed with 5% NaHCO₃ (5 X 1 mL), and dried (MgSO₄). Solvent was evaporated and the residue was purified by column chromatography using 5 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.41 g, 62%); m.p. 120-121 °C; ¹H-NMR (CDCl₃): δ 1.60-1.80 (m, 2 H), 2.31 (s, 3 H), 2.31-2.51 (m, 8 H), 3.32-3.43 (m, 2 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 6.77 (d, J = 8.8 Hz, 2 H), 7.02 (s, 1 H), 7.12 (d, J = 8.6 Hz, 2 H), 7.20-7.27 (m, 6 H), 7.41 (d, J = 8.6 Hz, 2 H), 8.11 (d, J = 8.8 Hz, 2 H), 9.76 (br t, 1 H, NH); Anal. Calcd. for C₃₅H₃₉N₅O₆S: C, 63.91; H, 5.98; N, 10.65. Found: C, 64.19; H, 6.22; N, 10.36.

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Example 7

a. 4-Ethoxycarbonyl-4-phenylpiperidine. To a stirred solution of H₂SO₄ (1.62 g, 16.56 mmol) in EtOH (200 mL), 4-phenyl-4-piperidine-carboxylic acid 4-methylbenzenesulfonate (25 g, 66.23 mmol) was added and the mixture was stirred and refluxed for 12 hours. Excess ethanol was evaporated at reduced pressure and the residue was poured into a mixture of ice and 6 N NaOH. The pH was adjusted to 10-11 by adding more 6 N NaOH and extracted with CH₂Cl₂ (3 X 100 mL). The combined CH₂Cl₂ extracts were dried (MgSO₄) and the solvent evaporated to leave the desired product as a colorless viscous oil, the ¹H-NMR showed it to be pure (14.68 g, 95%) and was used without any further purification.

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b. 3-(4-Ethoxycarbonyl-4-phenylpiperidin-1-yl)propylamine.

A mixture of 4-ethoxycarbonyl-4-phenylpiperidine (30.5 g, 0.131 mol), 3-bromopropylamine hydrobromide (42.93 g, 0.196 mol), potassium carbonate (36.14 g, 0.241 mole), and KI (10.8 g, 0.065 mol) in 1,4-dioxane (500 mL) was stirred and refluxed for 24 hours. Dioxane was

evaporated at reduced pressure, the residue was treated with ice-cold 6 N NaOH (400 mL) and extracted with CH₂Cl₂ (4 X 120 mL). Solvent was evaporated from the combined dried (K₂CO₃) CH₂Cl₂ extracts and the residue was purified by column chromatography on silica gel using CHCl₃/MeOH/2 M NH₃, in MeOH (20:2:1) as the eluent to afford the product as a viscous oil (24.2 g, 83.3%).

c. 1-{N-[3-(4-Ethoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1,2,3,6-tetra-hydro-2-thioxopyrimidine. This compound was prepared from 1,6-dihydro-5-methoxycarbonyl-2-[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenoxy)carbonyl]pyrimidine (0.592 g, 1 mmol), K₂CO₃ (0.276 g, 2 mmol), 3-[4-ethoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (0.350 g, 1.2 mmol, 1.2 eq), ethanethiol (0.5 mL), and TFA (0.5 mL) using the procedure described in Example 7 and purified by flash column chromatography (0.295 g, 47%); m.p. 125-126 °C; ¹H-NMR (CDCl₃): δ 1.13 (t, J = 7 Hz, 3 H), 1.62-1.80 (m, 2 H), 1.87-2.0 (m, 2 H), 2.06-2.18 (m, 2 H), 2.31 (s, 3 H), 2.34-2.39 (m, 2 H), 2.50-2.55 (m, 2 H), 2.79-2.83 (m, 2 H), 3.30-3.51 (m, 2 H), 3.74 (s, 3 H), 4.07 (q, J = 7 Hz, 2 H), 7.03 (s, 1 H), 7.18-7.36 (m, 6 H), 7.40 (d, J = 8.8 Hz, 2 H), 8.08 (d, J = 8.8 Hz, 2 H), 9.78 (br t, 1 H, NH); Anal. Calcd. for C₃₁H₃₇N₅O₇S: C, 59.70; H, 5.98; N, 11.23. Found: C, 59.55; H, 5.99; N, 11.43.

30 **Example 8**

1,6-Dihydro-1-{N-[3-(4,4-diphenylpiperidin-1-yl)propyl]carboxamido-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)pyrimidine. To a stirred mixture of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenoxy)carbonyl]pyrimidine (0.940 g, 2 mmol) and K₂CO₃ (0.552 g, 4 mmol) in anhydrous THF (20 mL) at room temperature under argon

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atmosphere, a solution of 3[4,4-diphenylpiperidin-1-yl] propylamine (0.882 g, 3 mmol, 1.5 eq) in THF (5 mL) was added and the stirring was continued for 1 hour. Solvent was evaporated from the reaction mixture, the residue was redissolved in CH₂Cl₂ (50 mL), washed with 5% NaHCO₃ (3 X 25 mL), brine (50 mL), and dried (MgSO₄). Solvent was evaporated and the residue was purified by flash chromatography on silica gel using 10% methanol in EtOAc as the eluent to give the desired product as an oil, which on trituration with hexane and drops of EtOAc became a white powder (1.10 g, 88%); m.p. 95-96 °C; ¹H-NMR (CDCl₃): δ 1.61-1.71 (m, 2 H), 2.26-2.33 (m, 2 H), 2.38 (s, 3 H), 2.39-2.50 (m, 8 H), 3.20-3.41 (m, 2 H), 3.65 (s, 3 H), 3.89 (s, 3 H), 6.65 (s, 1 H), 6.84 (br t, 1 H, NH), 7.08-7.29 (m, 10 H), 7.40 (d, J = 8.7 Hz, 2 H), 8.03 (d, J = 8.6 Hz, 2 H); Anal. Calcd. for C₃₅H₃₉N₅O₆.0.75 CH₂Cl₂: C, 62.28; H, 5.92; N, 10.16. Found: C, 62.23; H, 5.76; N, 10.12.

20 Example 9

5-Methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4,4-diphenyl-piperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

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1,6-Dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-6-(4-nitro-phenyl)pyrimidine.

A mixture of methyl 2-{(4-nitrophenyl)methylene}-3-oxobutyrate (12.46 g, 0.05 mol), O-methylisourea hydrogen sulfate (10.32 g, 0.06 mol), and NaOAc (9.84 g, 0.06 mol) in DMF (50 mL) was stirred and heated at 70-75 °C for 4 hours. The mixture was cooled and poured into ice-water (300 mL). The precipitate formed was filtered, washed with water, and dried. The crude product was purified by flash column chromatography on silica gel using 10% through 30% EtOAc in hexane as the gradient eluent (9.8 g, 64%). The ¹H-NMR analysis of

the product showed it to be a 19:1 mixture of the amine/imine tautomers which was used as such in the next step. $^1\text{H-NMR}$ (CDCl_3): δ 2.32, 2.38 (2 s, 3 H), 3.59, 3.70 (2 s, 3 H), 3.70, 3.85 (2 s, 3 H), 5.40, 5.66 (s, d, J = 3 Hz, 1 H), 5.50, 6.08 (s, d, J = 3 Hz, 1 H), 7.43, 7.45 (2 d, J = 9 Hz, 2 H), 8.10, 8.11 (2 d, J = 9 Hz, 2 H).

b. 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.

To a well-stirred mixture of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)pyrimidine (5.7 g, 0.0187 mol), NaHCO_3 (6.27 g, 0.074 mol), CH_2Cl_2 (200 mL), and water (50 mL) at 0-5 °C, 4-nitrophenyl chloroformate (3.76 g, 0.0186 mol) was added in 5 min and the mixture was allowed to warm to room temperature. After 10 hours, the TLC analysis of the reaction mixture showed the presence of a small amount of starting pyrimidine, therefore, more 4-nitrophenyl chloroformate (0.65 g, 0.0032 mol) was added and the stirring continued for an additional 4 hours. The two layers were separated, the CH_2Cl_2 layer was washed with saturated aqueous NaHCO_3 solution (3 X 50 mL), dried (MgSO_4), and the solvent evaporated. The residue was recrystallized from CH_2Cl_2 and hexane to give the product as white crystals (12.8 g, 89%); $^1\text{H-NMR}$ (CDCl_3): δ 2.48 (s, 3 H), 3.69 (s, 3 H), 3.94 (s, 3 H), 6.34 (s, 1 H), 7.36 (d, J = 9.1 Hz, 2 H), 7.46 (d, J = 8.7 Hz, 2 H), 8.14 (d, J = 8.7 Hz, 2 H), 8.26 (d, J = 9.1 Hz, 2 H); m.p. 168-169 °C. Anal. Calcd. for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_9$: C, 53.62; H, 3.86; N, 11.91. Found: C, 53.69; H, 3.92; N, 11.85.

c. 5-Methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4,4-di-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydro-pyrimidine.

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To a stirred solution of 1,6-dihydro-2-methoxy-6-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[N-[3-(4,4-diphenylpiperidin-1-yl)propyl]carboxamido]pyrimidine (0.208 g, 0.33 mmol) in THF (10 mL) at 5 °C under argon, 3 N HCl (6 mL) was added and the mixture was allowed to warm to room temperature. After 2 hours, solvents were evaporated completely, the residue was treated with 40 mL of 10% NaHCO₃, the product was extracted with CH₂Cl₂ (2 X 15 mL) and the combined extracts were dried (MgSO₄). Solvent was evaporated and the residue was crystallized from hexane and EtOAc (0.20 g, 97%); m.p. 197-198 °C; ¹H-NMR (CDCl₃): δ 1.63-1.67 (m, 2 H), 2.23-2.28 (m, 2 H), 2.34 (s, 3 H), 2.37-2.42 (m, 8 H), 3.20-3.41 (m, 2 H), 3.69 (s, 3 H), 6.75 (s, 1 H), 7.08-7.26 (m, 11 H), 7.46 (d, J = 8.7 Hz, 2 H), 8.08 (d, J = 8.7 Hz, 2 H), 8.77 (br t, 1 H, NH); Anal. Calcd. for C₃₄H₃₇N₅O₆: C, 66.76; H, 6.10; N, 11.45. Found: C, 66.48; H, 5.97; N, 11.25.

Example 10

1-[N-[3-(4-(4-Methoxyphenyl)-4-phenylpiperidin-1-yl)propyl]carboxamido]-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidin-4-one.

To a stirred mixture of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.47 g, 1 mmol) and K₂CO₃ (0.552 g, 4 mmol) in anhydrous THF (10 mL) at room temperature under argon atmosphere, a solution of 3-[4-(4-methoxyphenyl)-4-phenylpiperidin-1-yl]propyl-amine (0.390 g, 1.2 mmol, 1.2 eq) in THF (10 mL) was added and the stirring was continued for 2 hours. The solid was removed by filtration and the solution was cooled to 0-5 °C. 6N HCl (2 mL) was added to the solution and stirring was continued. After 3 hours, solvents were evaporated completely, the residue was redissolved in CH₂Cl₂ (20 mL), washed with 10% NaHCO₃ (2 X 10 mL), and dried (MgSO₄). Solvent was

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evaporated and the residue was purified by column chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.55 g, 86%); m.p. 100-102 °C;

5 $^1\text{H-NMR}$ (CDCl_3): δ 1.65-1.80 (m, 2 H), 2.26-2.31 (m, 2 H), 2.35 (s, 3 H), 2.39-2.44 (m, 6 H), 3.18-3.40 (m, 2 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 6.75 (s, 1 H), 7.60 (d, J = 8.7 Hz, 2 H), 6.84 (br s, 1 H, NH), 7.10 (d, J = 8.7 Hz, 2 H), 7.18-7.26 (m, 5 H), 7.46 (d, J = 8.6 Hz, 2 H), 8.08 (d, J = 8.6 Hz, 2 H), 8.78 (br t, 1 H, NH); Anal. Calcd. for $\text{C}_{35}\text{H}_{39}\text{N}_5\text{O}_7$: 0.12 CH_2Cl_2 , 0.12 EtOAc: C, 64.54; H, 6.12; N, 10.57. Found: C, 64.44; H, 6.12; N, 10.28.

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15 Example 11

1-{N-[3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (Scheme 2).

20 To a stirred mixture of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.47 g, 1 mmol), K_2CO_3 (0.276 g, 2 mmol) in anhydrous THF (10 mL) at room temperature under argon atmosphere, a solution of 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (0.332 g, 1.2 mmol, 1.2 eq) in THF (10 mL) was added and the stirring was continued for 2 hours. The solid was removed by filtration and the solution was cooled to 0-5 °C. To this, 6 N HCl (2 mL) was added and the stirring continued. After 3 hours, solvents were evaporated completely, the residue was redissolved in CH_2Cl_2 (20 mL), washed with 10% NaHCO_3 (2 X 10 mL), and dried (MgSO_4). Solvent was evaporated and the residue was purified by column chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.55 g, 86%); m.p. 180-181 °C; $^1\text{H-NMR}$ (CDCl_3): δ 1.60-

25

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35

1.80 (m, 2 H), 1.85-1.95 (m, 2 H), 2.03-2.10 (m, 2 H),
2.28-2.33 (m, 2 H), 2.35 (s, 3 H), 2.48-2.50 (m, 2 H),
3.20-3.40 (m, 2 H), 3.60 (s, 3 H), 3.68 (s, 3 H), 6.75
5 (s, 1 H), 7.20-7.34 (m, 6 H), 7.46 (d, $J = 8.8$ Hz, 2
H), 8.07 (d, $J = 8.8$ Hz, 2 H), 8.78 (br t, 1 H, NH);
Anal. Calcd. for $C_{30}H_{35}N_5O_8$: C, 60.70; H, 5.94; N, 11.80.
Found: C, 60.71; H, 5.99; N, 11.43.

Examples 11a & 11 b

10 (+)-1-[{N-[3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)
propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-
(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine and
(-)-1-[{N-[3-(4-Methoxycarbonyl-4-phenyl-piperidin-1-yl)
propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(4-
15 nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (Scheme
3).

a. (-)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-
methoxy-6-(4-nitro-phenyl)-1-[{N-[(2-phenyl)ethyl]}
20 carboxamidopyrimidine and (+)-1,6-Dihydro-2-methoxy-5-
methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[{N-[(2-
phenyl)ethyl]}carboxamidopyrimidine.

To a stirred solution of (+)-1,6-dihydro-2-methoxy-5-
25 methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitro-
phenyloxy)carbonyl]pyrimidine (2.66 g, 5.6 mmol) in
anhydrous THF (80 mL) at room temperature under argon
atmosphere, a solution of (S)-(-)- α -methylbenzylamine
0.82 g, 6.78 mmol, 1.2 eq) in THF (5 mL) was added and
the stirring was continued for 6 hours. Solvent was
30 evaporated from the reaction mixture, the residue was
redissolved in CH_2Cl_2 (50 mL), washed with 5% $NaHCO_3$ (3
 \times 25 mL), brine (50 mL), and dried ($MgSO_4$). Solvent was
evaporated and the residue was purified by flash
chromatography on silica gel using 5% to 30% EtOAc in
35 hexane as the gradient eluent. The first major product
to elute was (-)-1,6-dihydro-2-methoxy-5-methoxy-
carbonyl-4-methyl-6-(4-nitrophenyl)-1-[{N-[(2-phenyl)}

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ethyl}carboxamidopyrimidine and this compound was crystallized from isopropyl ether (0.85 g, 33.6%); m.p. 119-120 °C; $[\alpha]_D = -329.32$ (CH_2Cl_2 , 10.3 g/100 mL); $^1\text{H-NMR}$ (CDCl_3): δ 1.47 (d, $J = 7$ Hz, 3 H), 2.40 (s, 3 H), 3.61 (s, 3 H), 3.95 (s, 3 H), 4.96 (quint, $J = 6.5$ Hz, 2 H), 6.66 (s, 1 H), 6.82 (d, $J = 6.8$ Hz, 1 H, NH), 7.22-7.36 (m, 5 H), 7.43 (d, $J = 8.6$ Hz, 2 H), 8.09 (d, $J = 8.6$ Hz, 2 H); Anal. Calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_6$: C, 61.06; H, 5.35; N, 12.38. Found: C, 60.85; H, 5.13; N, 12.42.

10 The second major compound to elute was (+)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]}carboxamido pyrimidine and this compound was crystallized from isopropyl ether (0.92 g, 36.4%); m.p. 138-140 °C; $[\alpha]_D = +171.81$ (CH_2Cl_2 , 11.31 g/100 mL); $^1\text{H-NMR}$ (CDCl_3): δ 1.47 (d, $J = 7$ Hz, 3 H), 2.42 (s, 3 H), 3.644 (s, 3 H), 3.917 (s, 3 H), 4.989 (quint, $J = 6.5$ Hz, 2 H), 6.70 (s, 1 H), 6.81 (d, $J = 6.8$ Hz, 1 H, NH), 7.22-7.35 (m, 5 H), 7.36 (d, $J = 8.6$ Hz, 2 H), 8.04 (d, $J = 8.6$ Hz, 2 H); Anal. Calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_6$: C, 61.06; H, 5.35; N, 12.38. Found: C, 60.95; H, 5.20; N, 12.38.

b. (+)-1-{N-[3-(4-Methoxycarbonyl-4-phenyl piperidin-1-yl)propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydro pyrimidine.

A solution of (+)-1,6-dihydro-2-methoxy-5-methoxy carbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]}carboxamidopyrimidine (0.226 g, 0.5 mmol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.076 g, 0.5 mmol) in CH_2Cl_2 (10 mL) was stirred and refluxed for 4 hours and the solvent evaporated. The product was purified by column chromatography using 30% EtOAc in hexane as the eluent. The product was found to be a mixture of the amine-imine tautomers (0.120 g, 78.7%); $[\alpha]_D = +14.5$ (CH_2Cl_2 , 6 g/100 mL).

To a well-stirred solution of (+)-1,6-dihydro-5-methoxy carbonyl-2-methoxy-4-methyl-6-(4-nitrophenyl)pyrimidine (0.12 g, 0.393 mmol) and pyridine (0.5 mL) in CH₂Cl₂ (10 mL) at 0-5 °C, 4-nitrophenyl chloroformate (0.095 g, 0.472 mmol) was added in 5 min and the mixture was allowed to warm to room temperature. After 2 h, saturated aqueous NaHCO₃ solution (10 mL) was added and the stirring continued for 30 min. The two layers were separated, the CH₂Cl₂ layer was washed with saturated aqueous NaHCO₃ solution (3 X 5 mL), dried (Na₂SO₄), and the solvent evaporated. The residue was redissolved in THF (10 mL) and mixed with K₂CO₃ (0.11 g, 0.8 mmol). To this, a solution of 3-[4-methoxycarbonyl-4-phenyl piperidin-1-yl]propylamine (0.138 g, 0.5 mmol) in THF (5 mL) was added and the mixture was stirred for 2 hours. The solid was removed by filtration and the solution was cooled to 0-5 °C. To this, 6 N HCl (0.5 mL) was added and the stirring continued. After 3 hours, solvents were evaporated completely, the residue was redissolved in CH₂Cl₂ (20 mL), washed with 10% NaHCO₃ (4 X 5 mL), and dried (MgSO₄). Solvent was evaporated and the residue was purified by column chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.19 g, 82%); m.p. 138-140 °C; [α]_D = +108 (CH₂Cl₂, 6.65 g/100 mL); ¹H-NMR (CDCl₃): δ 1.60-1.80 (m, 2 H), 1.85-1.95 (m, 2 H), 2.03-2.10 (m, 2 H), 2.28-2.33 (m, 2 H), 2.35 (s, 3 H), 2.48-2.50 (m, 2 H), 3.20-3.40 (m, 2 H), 3.60 (s, 3 H), 3.68 (s, 3 H), 6.75 (s, 1 H), 7.20-7.34 (m, 5 H), 7.46 (d, J = 8.8 Hz, 2 H), 7.60 (br s, 1 H, NH), 8.07 (d, J = 8.8 Hz, 2 H), 8.78 (br t, 1 H, NH); Anal. Calcd. for C₃₀H₃₅N₅O₈.0.2 CH₂Cl₂.0.2 EtOAc: C, 59.27; H, 5.94; N, 11.15. Found: C, 59.07; H, 5.76; N, 10.99.

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c. (-)-1-{N-[3-(4-Methoxycarbonyl-4-phenyl piperidin-1-yl)propyl]carboxamido-5-methoxy

carbonyl-4-methyl-6-(4-nitrophenyl)-2-oxo-
1,2,3,6-tetrahydropyrimidine.

A solution of (-)-1,6-dihydro-2-methoxy-5-methoxy carbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[(2-phenyl) ethyl]}carboxamidopyrimidine (0.35 g, 0.774 mmol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.117 g, 0.774 mmol) in CH₂Cl₂ (10 mL) was stirred and refluxed for 8 hours and the solvent evaporated. The product was purified by column chromatography using 30% EtOAc in hexane as the eluent. The product, (-)-1,6-dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-6-(4-nitrophenyl)pyrimidine, was found to be a mixture of the amine-imine tautomers (0.170 g, 72%). To a well-stirred solution of (-)-1,6-dihydro-5-methoxy carbonyl-2-methoxy-4-methyl-6-(4-nitrophenyl)pyrimidine (0.152 g, 0.5 mmol) and pyridine (0.5 mL) in CH₂Cl₂ (10 mL) at 0-5 °C, 4-nitrophenyl chloroformate (0.121 g, 0.6 mmol) was added in 5 min and the mixture was allowed to warm to room temperature. After 2 hours, saturated aqueous NaHCO₃ solution (10 mL) was added and the stirring continued for 30 min. The two layers were separated, the CH₂Cl₂ layer was washed with saturated aqueous NaHCO₃ solution (3 X 5 mL), dried (Na₂SO₄), and the solvent evaporated. The residue was redissolved in THF (10 mL) and mixed with K₂CO₃ (0.165 g, 1.2 mmol). To this, a solution of 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (0.166 g, 0.6 mmol) in THF (5 mL) was added and the mixture was stirred for 2 hours. The solid was removed by filtration and the solution was cooled to 0-5 °C. To this, 6 N HCl (0.5 mL) was added and the stirring continued. After 3 hours, solvents were evaporated completely, the residue was redissolved in CH₂Cl₂ (20 mL), washed with 10% NaHCO₃ (4 X 5 mL), and dried (MgSO₄). Solvent was evaporated and the residue was purified by column chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized

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from hexane and EtOAc (0.19 g, 64%); m.p. 138-140 °C;
[α]_D = -106 (CH₂Cl₂, 3.95 g/100 mL); ¹H-NMR (CDCl₃): δ
1.60-1.80 (m, 2 H), 1.85-1.95 (m, 2 H), 2.03-2.10 (m,
2 H), 2.28-2.33 (m, 2 H), 2.35 (s, 3 H), 2.48-2.50 (m,
2 H), 3.20-3.40 (m, 2 H), 3.60 (s, 3 H), 3.68 (s, 3 H),
6.75 (s, 1 H), 7.20-7.34 (m, 6 H), 7.46 (d, J = 8.8 Hz,
2 H), 8.07 (d, J = 8.8 Hz, 2 H), 8.78 (br t, 1 H, NH);
Anal. Calcd. for C₃₀H₃₅N₅O₈.0.4 CH₂Cl₂: C, 58.18; H, 5.75;
N, 11.16. Found: C, 58.25; H, 5.67; N, 10.98.

10

Example 12

5-Methoxycarbonyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-4-methyl-6-(3,4-methylenedioxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine.

To a stirred solution of 5-benzyloxycarbonyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-4-methyl-6-(3,4-methylenedioxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (0.320 g, 0.48 mmol) in methanol (20 mL) and HCOOH (1 mL) at 0-5 °C, 10% Pd-C (0.26 g) was added in portions and the cooling bath was removed. TLC analysis of the reaction mixture at frequent intervals showed the completion of the reaction after 2 hours. The catalyst was removed by filtration and the solvent was evaporated to leave 1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-4-methyl-6-(3,4-methylenedioxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic acid as a white solid (0.275 g, 99%). The product was used in the next step without any further purification and characterization. A mixture of 1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-4-methyl-6-(3,4-methylenedioxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic acid (0.2 g, 0.346 mmol), 1-(3-dimethylamino propyl)-3-ethylcarbodiimide hydrochloride (0.382 g, 2 mmol), and 4-(N,N-dimethylamino)pyridine (0.488 g, 4

mmol), in methanol (20 mL) was stirred and refluxed for 5 h and the solvent evaporated. The residue was redissolved in CH₂Cl₂ (15 mL), washed with saturated aqueous ammonium chloride solution (3 X 10 mL), and dried (Na₂SO₄). Evaporation of the solvent left the pure product as white powder (0.202 g, 99%); m.p. 139-141 °C; ¹H-NMR (CDCl₃): δ 1.62-1.80 (m, 2 H), 1.95-2.20 (m, 4 H), 2.35 (s, 3 H), 2.30-2.55 (m, 4 H), 2.76-2.90 (m, 2 H), 3.21-3.40 (m, 2 H), 3.61 (s, 3 H), 3.67 (s, 3 H), 5.89 (s, 2 H), 6.61-6.82 (m, 3 H), 6.63 (s, 1 H), 7.21-7.35 (m, 6 H), 8.79 (br t, 1 H, NH); Anal. Calcd. for C₃₁H₃₆N₄O₈.0.3 EtOAc: C, 62.47; H, 6.25; N, 9.05. Found: C, 62.64; H, 6.25; N, 8.87.

15 **Example 13**

(+)-5-Carboxamido-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (Scheme 4).

20 a. **2-Cyanoethyl 3-{(4-nitrophenyl)methylene}-4-oxopentanoate.**

A mixture of ethyl propionylacetate (25 g, 0.173 mol) and 3-hydroxypropionitrile (18.48 g, 0.26 mol) was stirred and heated at 200-205 °C for 2 h and the ethanol formed was removed by distillation. The residue was subjected to high vacuum distillation and the fraction distilling at 120-125 °C at 0.4 mm of Hg was collected to get 2-cyanoethyl propionylacetate (21.5 g, 73.4%).

30 A mixture of 4-nitrobenzaldehyde (14.46 g, 0.957 mol), 2-cyanoethyl propionylacetate (17.0 g, 0.1005 mol), piperidine (0.41 g, 476 mL, 4.8 mmol), and acetic acid (0.288 g, 274 mL, 4.8 mmol) in 2-propanol (400 mL) was stirred at room temperature for 24 h. The white solid, 35 2-cyanoethyl 3-{(4-nitrophenyl)methylene}-4-oxo pentanoate, formed was filtered, washed with 2-propanol (2 X 50 mL) and dried (28.34 g, 97%); m.p. 98-100 °C.

b. 5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(4-nitrophenyl)pyrimidine.

A mixture of 2-cyanoethyl 3-{(4-nitrophenyl)methylene}-5-4-oxopentanoate (5.00 g, 16.54 mmol), O-methylisourea hydrogen sulfate (3.422 g, 19.85 mmol), and NaHCO₃ (2.78 g, 33.08 mol) in EtOH (70 mL) was stirred and heated at 85-90 °C for 5 h. The solid was removed by filtration and ethanol was evaporated from the filtrate. The residue was redissolved in EtOAc (300 mL), washed with water (2 X 100 mL), dried (Na₂SO₄), and the solvent evaporated. The crude product was purified by flash column chromatography on silica gel using CHCl₃/methanol (30:1) as the eluent, to leave the product as a white solid (2.95 g, 50%). The ¹H-NMR analysis of the product showed it to be a 5:1 mixture of the amine/imine tautomers and was used as such in the next step.

c. 5-(2-Cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.

To a well-stirred solution of 5-(2-cyanoethoxy carbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)pyrimidine (2.64 g, 7.36 mmol) and pyridine (1.19 mL, 14.72 mmol) in CH₂Cl₂ (100 mL) at 0-5 °C, 4-nitrophenyl chloroformate (1.485 g, 7.36 mmol) was added in 5 min and the mixture was allowed to warm to room temperature. After 16 h, saturated aqueous NaHCO₃ solution (25 mL) was added and the stirring continued for 30 min. The two layers were separated, the CH₂Cl₂ layer was washed with saturated aqueous NaHCO₃ solution (3 X 50 mL), dried (Na₂SO₄), and the solvent evaporated. The crude product was purified by flash column chromatography on silica gel using CHCl₃/EtOAc (25:1) as the eluent to give the product as a viscous oil (1.70 g, 44%); ¹H-NMR (CDCl₃): δ 1.24 (t, J = 7 Hz, 3 H),

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2.61-2.68 (m, 2 H), 2.88-2.92 (m, 2 H), 3.97 (s, 3 H),
4.32 (t, $J = 7$ Hz, 2 H), 6.34 (s, 1 H), 7.37 (d, $J =$
9.2 Hz, 2 H), 7.50 (d, $J = 8.7$ Hz, 2 H), 8.18 (d, $J =$
8.7 Hz, 2 H), 8.28 (d, $J = 9.2$ Hz, 2 H).

5

d. 5-(2-Cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]} carboxamidopyrimidine.

To a stirred solution of 5-(2-cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (17.5 g, 33.43 mmol) in anhydrous THF (200 mL) at room temperature under argon atmosphere, (R)-(+)-a-methylbenzylamine (4.86 g, 40.11 mmol) was added and the stirring was continued for 16 h. Solvent was evaporated from the reaction mixture and the residue was purified by flash chromatography on silica gel using toluene/EtOAc (20:3) as the eluent. The first major product to elute was (+)-5-(2-cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]} carboxamidopyrimidine and obtained as a viscous oil (6.11 g, 36.2%); $[\alpha]_D = +299.5$ ($c = 1.95$, CHCl_3); $^1\text{H-NMR}$ (CDCl_3): δ 1.18 (t, $J = 7$ Hz, 3 H), 1.47 (d, $J = 7$ Hz, 3 H), 2.61 (t, 2 H), 2.7-2.92 (m, 2 H), 3.98 (s, 3 H), 4.20-4.32 (m, 2 H), 4.96 (quint, $J = 6.5$ Hz, 2 H), 6.66 (s, 1 H), 6.82 (d, $J = 6.8$ Hz, 1 H, NH), 7.22-7.36 (m, 5 H), 7.45 (d, $J = 8.6$ Hz, 2 H), 8.11 (d, $J = 8.6$ Hz, 2 H). The second major compound to elute was (-)-5-(2-cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]} carboxamidopyrimidine and obtained as a viscous oil (5.92 g, 35%); $[\alpha]_D = -105.1$ ($c = 3.9$, CHCl_3); $^1\text{H-NMR}$ (CDCl_3): δ 1.20 (t, $J = 7$ Hz, 3 H), 1.48 (d, $J = 7$ Hz, 3 H), 2.62 (t, 2 H), 2.82 (q, 2 H), 3.94 (s, 3 H), 4.20-4.32 (m, 2 H), 4.96 (quint, $J = 6.5$ Hz, 2 H), 6.69 (s, 1 H), 6.84 (d, $J = 6.8$ Hz, 1 H, NH), 7.22-7.36 (m, 5 H), 7.39 (d, $J = 8.6$ Hz, 2 H), 8.06 (d, $J = 8.6$ Hz,

2 H).

e. (+)-5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(4-nitrophenyl)pyrimidine.

5 To a stirred solution of (+)-5-(2-cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]}carboxamido pyrimidine (2.62 g, 5.182 mmol) in toluene (40 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.237, 1.55 mmol) at room temperature and the resulting solution was heated at 90 °C for 3.5 minutes. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel using 9:1 CHCl₃/EtOAc as the eluent, to give 1.32 g (71%) of (+)-5-(2-cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(4-nitrophenyl)pyrimidine; [α]_D = +4.0 (c = 3.25, CHCl₃).

f. (+)-5-(2-Cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy) carbonyl]pyrimidine.

To a well-stirred solution of 5-(2-cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl) pyrimidine (1.62 g, 4.52 mmol) and 4-(N,N-dimethylamino)pyridine (0.663 g, 5.43 mmol) in CH₂Cl₂ (50 mL) at 0-5 °C, 4-nitrophenyl chloroformate (1.094 g, 5.43 mmol) was added in 5 minutes and the mixture was allowed to warm to room temperature. After 3 hours the solvent evaporated and the product was purified by flash column chromatography on silica gel using CHCl₃/EtOAc (25:1) as the eluent to give the product as a white solid (2.25 g, 95%); ¹H-NMR (CDCl₃): δ 1.24 (t, J = 7 Hz, 3 H), 2.61-2.68 (m, 2 H), 2.88-2.92 (m, 2 H), 3.97 (s, 3 H), 4.32 (t, J = 7 Hz, 2 H), 6.34 (s, 1 H), 7.37 (d, J = 9.2 Hz, 2 H), 7.50 (d, J = 8.7 Hz, 2 H), 8.18 (d, J = 8.7 Hz, 2 H), 8.28 (d, J = 9.2 Hz, 2 H);

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$[\alpha]_D = +317.2$ ($c = 3.9$, CHCl_3).

g. (+)-5-(2-Cyanoethoxycarbonyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]} carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydro pyrimidine.

To a stirred mixture of (+)-5-(2-cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (3.60 g, 6.878 mmol) in anhydrous THF (100 mL) at room temperature under argon atmosphere, a solution of 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (2.47 g, 8.94 mmol, 1.3 eq) in THF (10 mL) was added and the stirring was continued for 12 hours. The mixture was cooled to 0 °C and aqueous 6N hydrochloric acid (10 mL). The mixture was allowed to warm to room temperature and the stirring was continued for 5 h. Solvent was evaporated from the reaction mixture, the residue was purified by flash chromatography on silica gel using ethyl acetate (800 mL) followed by chloroform-methanol-2M ammonia in methanol (90/8/4) as the eluent, to obtain the desired product as a white powder (4.40 g, 98.5%); $^1\text{H-NMR}$ (CDCl_3): δ 1.23 (t, $J = 7.5$ Hz, 3 H), 2.0-2.1 (m, 2 H), 2.40-2.95 (m, 12 H), 3.25-3.50 (m, 4 H), 3.65 (s, 3 H), 4.27-4.32 (m, 2 H), 6.64 (s, 1 H), 7.20-7.33 (m, 5 H), 7.49 (d, $J = 7.8$ Hz, 2 H), 8.08 (d, $J = 7.8$ Hz, 2 H), 8.70-8.90 (m, 2 H); $[\alpha]_D = +112.1$ ($c = 2.15$, CHCl_3); This product was used in the next step without any additional analysis.

h. (+)-5-Carboxamido-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine.

To a stirred solution of 5-(2-cyanoethoxycarbonyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenyl

piperidin-1-yl)propyl}carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrhydropyrimidine (4.40 g, 6.8 mmol) in acetone (50 mL) at 0 °C, sodium hydroxide solution (1 N, 27.2 mL, 4 eq.) was added drop wise and the stirring was continued until the disappearance of the starting material (1 hour). Most of the acetone from the mixture was evaporated under reduced pressure while keeping the temperature at 0 °C and the residue was adjusted to pH 7.0 by the addition of 1N hydrochloric acid. The white precipitate of (+)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrhydro pyrimidine-5-carboxylic acid formed was filtered and dried under vacuum (3.59 g, 89%). $^1\text{H-NMR}$ (CDCl_3): δ

A mixture of (+)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic acid (0.350 g, 0.59 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.2264 g, 1.181 mmol, 2 eq.), and 4-(N,N-dimethylamino)pyridine (0.1443 g, 1.181 mmol, 2 eq) in anhydrous dichloromethane was stirred at room temperature for 2 h. To this, 40% aqueous ammonia (0.6 mL) was added and the stirring was continued for 12 h. The mixture was diluted with 100 mL of dichloromethane and washed with saturated aqueous ammonium chloride solution (3 X 20 mL). Solvent was evaporated from the dried (magnesium sulfate) dichloromethane solution and the residue was purified by column chromatography on silica gel using

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chloroform-methanol-2M ammonia in methanol (500/16/8) as the eluent, to obtain the desired product as a white powder (0.24 g, 69%); m.p. 107-109 °C; ¹H-NMR (CDCl₃): δ 1.20 (t, J = 7.5 Hz, 3 H), 1.66-1.72 (m, 2 H), 1.79-2.00 (m, 3 H), 2.00-2.20 (m, 2 H), 2.29-2.35 (m, 2 H), 2.42-2.60 (m, 2 H), 2.62-2.82 (m, 3 H), 3.20-3.40 (m, 2 H), 3.60 (s, 3 H), 5.70 (br s, 2 H, NH₂), 6.59 (s, 1 H), 7.20-7.39 (m, 6 H), 7.52 (d, J = 7.8 Hz, 2 H), 8.13 (d, J = 7.8 Hz, 2 H), 8.82 (t, 1 H); [α]_D = +115.71 (c = 1.4, CHCl₃); Anal. Calcd. for C₃₀H₃₆N₆O₇.0.8 H₂O: C, 59.36; H, 6.24; N, 13.84. Found: C, 59.47; H, 6.07; N, 13.64.

Example 14

15 (+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine (Scheme 5).

20 a. **Benzyl 3-[(3,4-difluorophenyl)methylene]-4-oxopentanoate.** A solution of benzyl propionylacetate (36.3 g, 176 mmol), 3,4-difluorobenzaldehyde (25.0 g, 176 mmol), piperidine (0.86 mL, 9.0 mmol) and acetic acid (0.49 mL, 9.0 mmol) were refluxed with removal of water using Dean-Stark apparatus for 5h. The solvent was removed in vacuo and the residue was dissolved in EtOAc. It was washed with water (100 mL) followed by brine (100 mL) and dried over anhydrous Na₂SO₄. Solvent was evaporated to get pale yellow syrup (60.2 g). It was used in the next step without further purification.

35 b. **5-(Benzylloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine.** A suspension of benzyl 3-[(3,4-difluorophenyl)methylene]-4-oxopentanoate (16.0 g, 48.0 mmol), O-methylisourea hydrogen sulfate (16.65 g, 97.02 mmol), NaHCO₃ (16.3 g,

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130.2 mmol) in DMF (190 mL) was stirred at 70°C for 20h. After cooling to room temperature, the mixture was filtered and the filtrate was diluted with EtOAc (300 mL) and then washed with water (4X100 mL), brine (200 mL) and dried over Na₂SO₄. After removal of solvent, the residue was purified by column chromatography (SiO₂, EtOAc/Hexane, 10%-30%) to get 5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-methyl-6-(3,4-difluorophenyl)pyrimidine as a colorless oil (10.6 g, 58%). The NMR analysis showed it to be a mixture of amine/imine tautomers and was used as is in the next step.

c. 5-(Benzylloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine. To a well stirred solution of 5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine (17.0 g, 44.04 mmol) and 4-dimethylaminopyridine (6.99 g, 57.25 mmol) in CH₂Cl₂ (200 mL) was added a powder of 4-nitrophenyl chloroformate 11.54 g, 57.25 mmol) at room temperature. The reaction mixture was stirred for 12 hours and then the solvent was removed in vacuo. The residue was purified by chromatography (SiO₂, EtOAc/Hexane 10-30%) to get 5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine as a colorless viscous oil (12.6 g, 50%). ¹H NMR (CDCl₃): δ 1.24 (t, J=7.2 Hz, 3H), 2.81-2.98 (m, 3H), 3.97 (s, 3H), 5.14 (AB_q, δ_A=5.08, δ_B=5.20, J=12.3 Hz, 2H), 6.28 (s, 3H), 7.03-7.29 (m, 8H), 7.35 (d, J=9.2 Hz, 2H), 8.26 (d, J=9.2 Hz, 2H).

d. 5-(Benzylloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine. To a stirred mixture of 5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-

(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (12.6 g, 22.86 mmol) in THF (150 mL) was added a solution of R-(+)-a-methyl benzylamine (3.53 mL, 27.44 mmol) at room temperature. The stirring was continued for 12 hours. Solvent was removed in vacuo. The yellow residue was dissolved in chloroform (200 mL) and was washed with 10% K₂CO₃ solution (2x30 mL). The organic layer was dried over Na₂SO₄, filtered and solvent was removed in vacuo. The resulting mixture of diastereomers was separated by column chromatography over silica gel with 9:1 Pet. ether:Ether to 4:1 Pet. ether:Ether. First major product to elute was (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine. Colorless oil, R_f= 0.31(4:1 Pet ether:ether), wt.= 3.8 g (60%), [α]_D = +267.05 (c = 0.76, CHCl₃) ¹H NMR: δ 1.22 (t, J=7.5 Hz, 3H), 1.52 (d, J=6.9 Hz, 3H), 2.88 (q, J=6.0 Hz, 2H), 3.99 (s, 3H), 4.99 (m, 1H), 5.09 (AB_q, δ_A=5.00, δ_B= 5.19, J= 12.6 Hz, 2H), 6.66 (s, 1H), 6.99-7.36 (m, 13H); Second major product to elute was (-)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine. Colorless oil. R_f= 0.22(4:1 Pet ether:ether), wt.= 3.2 g (51.2%), [α]_D = -146.89 (c = 0.38, CHCl₃) ¹H NMR: δ 1.22 (t, J=7.2 Hz, 3H), 1.49 (d, J=6.6 Hz, 3H), 2.88 (q, J=6.0 Hz, 2H), 3.94 (s, 3H), 5.03 (m, 1H), 5.11 (AB_q, δ_A=5.02, δ_B= 5.19, J= 12.6 Hz, 2H), 6.68 (s, 1H), 6.91-7.34 (m, 13H).

e. (+)-5-(Benzylloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine. To a stirred solution of (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (1.83 mmol, 1.0 g) in toluene (10 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.81 mmol, 0.12 mL) at room temperature and

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the resulting solution was heated to reflux for 5 h and then stirred for 12 h at room temperature. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with 3:1 EtOAc/Hexanes as the eluting system. 0.56 g of the (+)-5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine was obtained (77%).

f. (+)-5-(Benzylloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy) carbonyl]pyrimidine. To a well stirred solution of (+)-5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine (17.0 g, 44.04 mmol) and 4-dimethylaminopyridine (6.99 g, 57.25 mmol) in CH₂Cl₂ (200 mL) was added a powder of 4-nitrophenyl chloroformate 11.54 g, 57.25 mmol) at room temperature. The reaction mixture was stirred for 12 hours and then the solvent was removed in vacuo. The residue was purified by chromatography (SiO₂, EtOAc/Hexane 10-30%) to get (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy) carbonyl]pyrimidine as a colorless viscous oil (19.3 g, 76%).

g. (+)-5-(Benzylloxycarbonyl)-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenyl piperidin-1-yl)propyl]carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine. To a stirred mixture of (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy) carbonyl]pyrimidine (0.55 g, 1.12 mmol) in THF (5 mL) was added a solution of 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (0.31 g, 1.12 mmol) in THF (5 mL) at room temperature. The stirring was continued for 12 hours. A solution of 10% HCl in water (2 mL) was added and stirred for 2 h. The solvent was

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then removed in vacuo and the residue was extracted with ethyl acetate (3 X 10 mL). It was washed with 10% aq. KOH solution, dried over Na₂SO₄, and solvent was removed in vacuo to obtain (+)-5-(benzyloxycarbonyl)-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]} carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine as a white foamy compound (0.73 g, 96.6%) the purity of which was characterized as its HCl salt. It was used in the next step without further purification. Anal. Calcd. for C₃₁H₄₁ClF₂N₄O₆.0.5CHCl₃:C, 58.43; H, 5.43; N, 7.27. Found: C, 58.11, H; 5.85; N, 7.64.

h. 6-(3,4-Difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxy carbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid. To a suspension of 10% Pd-C (0.14 g, 20% by wt.) in MeOH (3 mL) was added the solution of (+)-5-(benzyloxycarbonyl)-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl) propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine at room temperature with constant stirring. A balloon filled with H₂ was attached and the reaction mixture was stirred for 48 hours. The black suspension was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 10% MeOH in EtOAc) to obtain (+)-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl) propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid as a white solid. M.P. 184-186 °C; [α]_D = +142.2 (c = 0.25, CHCl₃) The purity was checked by combustion analysis as a HCl salt. Anal. Calcd. for C₃₀H₃₅ClF₂N₄O₆.0.3CHCl₃:C, 55.40; H, 5.42; N, 8.53. Found: C, 55.34; H; 5.80; N, 8.13.

i. (+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-ethyl-

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1-[N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-2-oxo-1,2,3,6-tetrahydro pyrimidine.

To a solution of (+)-6-(3,4-difluorophenyl)-4-ethyl-
5 1-[N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-
5-carboxylic acid (0.22 g, 0.375 mmol) in CH₂Cl₂ (3 mL)
was added 4-N,N-dimethylamino pyridine (0.14 g, 1.12
mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
10 hydrochloride (0.21 g, 1.12 mmol) under argon and the
resulting solution was stirred at room temperature for
2h. Three drops of saturated NH₄OH was then added and
the solution was stirred for 48 h. The solution was
washed with water (5 ml) and dried over Na₂SO₄. The
15 solvent was removed in vacuo and the residue was
purified by column chromatography (SiO₂, 10% MeOH in
CHCl₃) to obtain 5-carboxamido-6-(3,4-difluorophenyl)-4-
ethyl-1-[N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-2-oxo-
20 1,2,3,6-tetrahydropyrimidine as a beige solid (0.1 g,
45%). Characterized as HCl salt. M.P. 136-138°C., [α]_D
= +111.44 (c = 0.18, MeOH): δ 1.21 (t, J=7.5 Hz, 3H),
1.60-1.75 (m, 2H), 1.92-2.1 (m, 8H), 2.33 (t, J=6.6 Hz,
2H), 2.44-2.52 (m, 2H), 2.53-2.84 (m, 4H), 3.27-3.32
25 (m, 2H), 3.60 (s, 3H), 5.60 (br s, 2H), 6.47 (s, 1H),
7.05-7.33 (m, 8H), 8.80 (br t, 1H), Anal. Calcd. for
C₃₀H₃₅ClF₂N₄O₆·1.0 CHCl₃: C, 50.35; H, 5.04; N, 9.47.
Found: C, 50.40; H, 5.33; N, 9.13.

30 Example 15

6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-
oxo-1-[N-[4-(2-pyridyl)-piperidin-1-yl]propyl]carboxamido-1,2,3,6-tetrahydropyrimidine
dihydrochloride (Scheme 7).

35

a. 1-Benzyl-4-cyano-4-(2-pyridyl)piperidine. To a
mixture of N,N-bis-(2-chloroethyl)benzylamine

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- (E.Szarvasi, Eur. J. Med. Chem. Ther. 11(2), 115-124, 1976) (60 g, 22 mmol), 2-pyridylacetonitrile (2.51 ml, 22 mmol) and tetrabutylammonium hydrogen sulfate (0.26 g, 0.7 mmol) in toluene (10 ml), sodium hydroxide solution (2.43 g in 4.86 ml H₂O) was added over a 20 minute period. The reaction mixture was heated at 65 °C for 4 hours. The reaction mixture was cooled to room temperature, 10 ml of water was added and the solution partitioned between ethyl acetate (45 ml) and water.
- 5 The organic layer was dried over sodium sulfate, filtered and concentrated. Purification of the crude product by column chromatography (hexane:EtOAc, 2:3) gave 6.2 g (87%) of the title compound as a red solid;
- 10 ¹H-NMR (CDCl₃): δ 2.05 (d, J = 13.1 Hz, 2 H), 2.30 (t, J = 13.2 Hz, 2 H), 2.48 (t, J = 13.2 Hz, 2 H), 2.97 (d, J = 12.1 Hz, 2 H), 3.57 (s, 2 H), 7.19-7.27 (m, 6 H), 7.30 (d, J = 7.6 Hz, 1 H), 7.60 (t, J = 7.6 Hz, 1 H), 8.58 (d, J = 4.6 Hz, 1H).
- 15
- 20 b. **1-Benzyl-4-carboxamido-4-(2-pyridyl)piperidine.** To 1-benzyl-4-cyano-4-(2-pyridyl)piperidine (4.5 g, 14.3 mmol), 10 ml of conc.H₂SO₄ was added and the solution was stirred at room temperature for 24 hours. It was cooled to 0 °C, diluted with ice pieces and poured into crushed ice. The mixture was then carefully neutralized with 50 % NaOH solution. The reaction mixture was repeatedly extracted with chloroform (3 x 25 ml), dried over sodium sulfate, filtered and concentrated to give 4.5 g (95%) of the crude product which was used as such for the subsequent step; ¹H-NMR (CDCl₃): δ 2.21-2.28 (m, 2 H), 2.47 (s, 6 H), 3.41 (s, 2 H), 5.23 (s, 1 H), 6.40 (s, 1 H), 7.12-7.29 (m, 6 H), 7.33 (d, J = 7.6 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H), 8.55 (d, J = 4.6 Hz, 1 H).
- 25
- 30
- 35 c. **1-Benzyl-4-(2-pyridyl)-piperidine.** To 1-benzyl-4-carboxamido-4-(2-pyridyl)piperidine (4.5 g, 13.5 mmol)

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in anhydrous methanol (100 ml), HCl gas was bubbled through the solution at 0 °C for 15 minutes. The reaction mixture was then refluxed for 24 hours. It was cooled to room temperature, concentrated, neutralized with 50 % NaOH and repeatedly extracted with chloroform (3 x 25 ml). The combined organic layer was then dried over sodium sulfate, filtered and concentrated. Flash chromatography (hexane:ethylacetate, 1:4) of the crude product yielded 1.72 g (50%) of the product as a syrup; ¹H-NMR (CDCl₃): δ 1.8-1.94 (m, 4 H), 2.11 (t, J = 11.4 Hz, 2 H), 2.70-2.72 (m, 1 H), 3.02 (d, J = 11.4 Hz, 2 H), 3.54 (s, 2 H), 7.07-7.36 (m, 7 H), 7.58 (t, J = 7.6 Hz, 1 H), 8.52 (d, J = 4.6 Hz, 1 H).

d. 3-[4-(2-Pyridyl)-piperidine-1-yl]propylamine (Scheme 6). To 1-Benzyl-4-(2-pyridyl)-piperidine (3.26 g, 12.9 mmol) in dry methanol (25 ml), 10% palladium hydroxide (1.9 g) was added and the solution was hydrogenated at 200 psi for 24 hours. The solution was filtered over celite, concentrated to give 2.1 g (99%) of 4-(2-pyridyl)-piperidine which was used as such for the subsequent step. A mixture of 3-bromopropylamine hydrobromide (20 g, 91.3 mmol), potassium carbonate (37.85 g, 273.9 mmol) and di-tert-butyldicarbonate (21.90 g, 100 mmol) in methanol was stirred at room temperature for 24 hours. The reaction mixture was concentrated and partitioned between 250 ml EtOAc and 50 ml water, dried over sodium sulfate, filtered and concentrated. Purification of the crude product by column chromatography (Hexane: EtOAc, 4.5:0.5) gave 17.5 g (80%) of the product as a pale yellow oil. To a stirred solution of the 4-(2-pyridyl)-piperidine (1.86 g, 11.4 mmol) in dioxane (20 ml), N-(tert-butoxycarbonyl)-3-bromopropylamine (2.82 g, 11.4 mmol) and potassium carbonate (3.16 g, 22.9 mmol) were added and the solution refluxed for 24 hours. The reaction

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mixture was cooled to room temperature, concentrated and partitioned between 40 ml chloroform and 5 ml water. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product
5 was purified by column chromatography (ethyl acetate:methanol, 4:1) to yield 1.86 g (49 %) of the required product as a colorless oil; $^1\text{H-NMR}$ (CDCl_3): δ 1.45 (s, 9 H), 1.54-1.69 (m, 8 H), 2.21-2.68 (m, 2 H), 2.74-2.80 (m, 1 H), 3.02-3.22 (m, 4 H), 5.41 (s, 1H), 7.13-7.17 (m, 1 H), 7.33 (d, $J = 7.93$ Hz, 1 H), 7.63 (t, $J = 7.6$ Hz, 1 H), 8.54 (d, $J = 4.6$ Hz, 1 H). To N-(tert-butoxycarbonyl)-3-[4-(2-pyridyl)-piperidin-1-yl]propylamine (0.15g, 0.45 mmol) in 5 ml of dichloromethane, 1 ml of trifluoroacetic acid was added
10 and the solution stirred at room temperature for 1 hour. The solution was concentrated, neutralized with 10 % KOH solution and extracted into 25 ml of dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated to give 0.098 g (100%) of 3-[4-(2-pyridyl)-piperidin-1-yl]propylamine
15 which was used as such for the subsequent step (step h).

e. **Methyl 2-{(3,4-difluorophenyl)methylene}-3-oxobutyrate.** A mixture of 3,4-difluorobenzaldehyde (14.2 g, 0.1 mol), methyl acetoacetate (12.2 g, 0.105 mol), piperidine (0.430 g, 5 mmol), and acetic acid (0.30 g, 5 mmol) in benzene (150 mL) was stirred and refluxed with a Dean-Stark trap for 8 hours. Benzene
20 was evaporated, the residue was dissolved in ethyl acetate (200 mL) and washed with brine (50 mL), saturated potassium bisulfate solution (50 mL), and saturated sodium bicarbonate solution in sequence. The ethyl acetate solution was dried (magnesium sulfate),
25 solvent removed under reduced pressure and the residue was purified by column chromatography (SiO_2 , EtOAc/hexane , 10%-15%). The product, methyl 2-{(3,4-

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difluorophenyl)methylene}-3-oxobutyrate, was obtained as a yellow oil (0.98 g, 98.3%) and was used in the next step without any further characterization.

5 f. *6-(3,4-Difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine.* A mixture of methyl 2-{(3,4-difluorophenyl)methylene}-3-oxobutyrate (8.8 g, 36.6 mmol), O-methylisourea hydrogen sulfate (9.4 g, 55 mmol), and NaHCO₃ (12.3 g, 0.146 mol) in DMF (30 mL) was stirred and heated at 70 °C for 16 hours. The mixture was cooled, diluted with EtOAc (300 mL) and washed with water (5 X 300 mL), brine (300 mL), and dried (MgSO₄). Solvent was evaporated and the crude product was purified by flash column chromatography on silica gel using 10% through 20% EtOAc in hexane as the gradient eluent, to leave the product as an oil (3.82 g, 30.2%); ¹H-NMR (CDCl₃): δ 2.32, 2.39 (2 s, 3 H), 3.58, 3.64 (2 s, 3 H), 3.72, 3.85 (2 s, 3 H), 5.55 (s, 1 H), 6.13-7.8 (m, 4 H).

20 g. *6-(3,4-Difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.*

25 To a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine (2.82 g, 9.52 mmol) and 4-dimethylaminopyridine (1.16 g, 9.52 mmol) in CH₂Cl₂ (50 mL), at 0-5 °C, 4-nitrophenyl chloroformate (1.82 g, 9.04 mmol) was added and the mixture was allowed to warm to room temperature. After 30 12 hours solvent was evaporated and the residue was purified by flash column chromatography (SiO₂, EtOAc/hexane, 10%-15%) to obtain the product as white crystals (3.72, 84.7%); m.p. 172-174 °C; ¹H-NMR (CDCl₃): δ 2.51 (s, 3 H), 3.72 (s, 3 H), 3.97 (s, 3 H), 6.26 (s, 1 H), 7.0-7.3 (m, 3 H), 7.38 (d, J = 9.3 Hz, 2 H), 8.32 (d, J = 9.3 Hz, 2 H).

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h. 6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-
oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]propyl}
carboxamido-1,2,3,6-tetrahydropyrimidine
dihydrochloride. To 6-(3,4-difluorophenyl)-1,6-
5 dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-
nitrophenoxy)carbonylpyrimidine (0.04 g, 0.086 mmol) in
10 ml of dry dichloromethane, 3-[4-(2-pyridyl)-
piperidine-1-yl]propylamine (0.038 g, 0.17 mmol) was
added and the solution was stirred at room temperature
10 for 24 hours. The reaction mixture was stirred for
another 1 hour after addition of 2 ml of 6N HCl. After
neutralization with 10% aqueous KOH solution, the
reaction mixture was extracted into dichloromethane (3
x 10 ml). The organic layer was dried over sodium
15 sulfate, filtered and concentrated. The crude product
was purified by flash chromatography (EtOAc: MeOH,
4.5:0.5) to give 0.040 g (89%) as a syrup; ¹H-NMR
(CDCl₃): δ 1.73-2.11 (m, 7 H), 2.41 (s, 6 H), 2.69 (m,
1 H), 3.04 (d, J = 12.1 Hz, 2 H), 3.31-3.48 (m, 2 H),
20 3.71 (s, 3 H), 6.70 (s, 1 H), 7.24-7.27 (m, 5 H), 7.61
(t, J = 8.0 Hz, 2 H), 8.51 (d, J = 4.6 Hz, 1 H), 8.89
(t, J = 5.1 Hz, 2 H).

25 To the free base (0.04g, 0.07 mmol) in 4 ml of
dichloromethane, 5 ml of 1N HCl in ether was added, and
the solution concentrated under reduced pressure.
Recrystallization from ether gave 0.046 g (98%) of 6-
(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-
1-{N-[4-(2-pyridyl)-piperidine-1-yl]propyl}carboxamido-
30 1,2,3,6-tetrahydropyrimidine dihydrochloride as a white
solid; m.p. 170-174 °C; Anal. Calcd. for
C₂₇H₃₃Cl₂F₂N₅O₄.1.0 H₂O: C, 52.43; H, 5.70, N 11.30. Found:
C, 52.16; H 5.35; N 11.10.

35 Example 16

6-(3,4-Benzofurazan-5-yl)-5-methoxycarbonyl-4-methyl-2-
oxo-1-{N-[4-(2-pyridyl)-piperidin-1-yl]propyl}carbox

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amido-1,2,3,6-tetrahydropyrimidine dihydrochloride
(Scheme 8).

5-Methylbenzfuroxan. 4-Methyl-2-nitroaniline (100 g, 0.650 mol) was suspended in saturated alcoholic sodium hydroxide solution (1.50 l). To this suspension was added with cooling (5 °C) commercial aqueous sodium hypochlorite till the red color disappeared. The fluffy yellow precipitate formed was filtered, washed with cold water and recrystallized from ethanol to get 5-Methylbenzfuroxan (88.2 g, 89 % yield) as a pale solid.

5-Methylbenzofurazan. To 5-Methylbenzfuroxan (88.2 g, 0.59. mol) in refluxing EtOH (75 ml) was added dropwise P(OEt)₃, (150 ml). When addition was complete, refluxing was continued for 1 more hour. The solvent was removed by rotary evaporation and the residue shaken with water (200 mL) and allowed to stand overnight at (0-5 °C). The brown solid so obtained was filtered, washed with water and chromatographed on silica gel to yield 5-Methylbenzofurazan (70 g, 87 %) as white needle.

5-Dibromomethylbenzofurazan. 5-Methylbenzofurazan (70 g, 0.52 mol), NBS (325 g), and benzoyl peroxide (0.5 g) were refluxed with stirring in carbon tetrachloride (1.5 L) with exclusion of moisture for 30 hours. The reaction mixture was washed with water (2X0.5L), dried (NaSO₄), and the solvent was removed in vacuo. The residue was chromatographed (silica, EtOAc-hexane, 1:150) to give 122 g (80%) of the title compound. The resulting white solid was used in the next step without any further characterization.

35

5-Formylbenzofurazan. To a refluxing mixture of the dibromomethylbenzofurazan (122 g, 418 mmol) in EtOH (1

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L) was added AgNO₃ (163 g) in 2 L of water. Refluxing was continued for 2 hours. The mixture was cooled and the AgBr was removed by filtration through Celite, and the solvent was concentrated to a small volume. The 5 resulting solution was extracted with toluene (10 X 100 mL), dried (MgSO₄), and the solvent was removed in vacuo. The residue was chromatographed on silica (EtOAc-hexane, 8:1000) to give 48.2 g of the title aldehyde (78%) as a white solid.

10

a. **Methyl 2-{(benzofuran-5-yl)methylene}-3-oxobutyrate.**

A mixture of 5-Formylbenzofurazan (0.6 g, 4.1 mmol), methyl acetoacetate (0.52 g, 4.5 mmol), piperidine (0.019 g, 0.225 mmol), and acetic acid (0.014 g, 0.225 mmol) in benzene (30 mL) was stirred and refluxed with a Dean-Stark trap for 8 h. Benzene was evaporated, the residue was dissolved in ethyl acetate (80 mL) and washed with brine (50 mL), saturated potassium bisulfate solution (50 mL), and saturated sodium bicarbonate solution in sequence. The ethyl acetate solution was dried (magnesium sulfate), solvent removed under reduced pressure and the residue was purified by column chromatography (SiO₂, EtOAc/hexane, 10%-15%). The product, methyl 2-{(benzofuran-5-yl)methylene}-3-oxobutyrate, was obtained as an oil (0.98 g, 98.3%) and was used in the next step without any further characterization.

30

b. **6-(Benzofuran-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine.** A mixture of methyl 2-{(benzofuran-5-yl)methylene}-3-oxobutyrate (1.02 g, 4.1 mmol), O-methylisourea hydrogen sulfate (1.06 g, 6.2 mmol), and NaHCO₃ (1.3 g, 16.4 mmol) in DMF (15 mL) was stirred and heated at 70 °C for 16 h. The mixture was cooled, diluted with EtOAc (50 mL) and washed with water (5X 50 mL), brine (50 mL), and dried

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(MgSO₄). Solvent was evaporated and the crude product was purified by flash column chromatography on silica gel using 10% through 20% EtOAc in hexane as the gradient eluent, to leave the product as an oil (0.52 g, 43%); ¹H-NMR (CDCl₃): δ 2.38, 2.42 (2 s, 3 H), 3.60, 3.66 (2 s, 3 H), 3.74, 3.82 (2 s, 3 H), 5.53, 5.68 (2 s, 1 H), 6.31, 6.32 (br s, 1 H), 7.0-7.8 (m, 3 H).

c. **6-(Benzofuran-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.**

To a solution of 6-(benzofuran-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine (0.485 g, 1.6 mmol) and 4-dimethylaminopyridine (0.2 g, 1.6 mmol) in CH₂Cl₂ (20 mL), at 0-5 °C, was added 4-nitrophenyl chloroformate (0.307 g, 1.52 mmol) and the mixture was allowed to warm to room temperature. After 12 hours solvent was evaporated and the residue was purified by flash column chromatography (SiO₂, EtOAc/hexane, 10%-15%) to obtain the product as white crystals (0.665 g, 89%); m.p. 180-183 °C; ¹H-NMR (CDCl₃): δ 2.54 (s, 3 H), 3.75 (s, 3 H), 3.98 (s, 3 H), 6.37 (s, 1 H), 7.40 (d, J = 9.3 Hz, 2 H), 7.52 (d, J = 9.0 Hz, 1 H), 7.68 (s, 1 H), 7.84 (d, J = 9.0 Hz, 1 H), 8.32 (d, J = 9.3 Hz, 2 H).

d. **6-(3,4-Benzofuran-5-yl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidin-1-yl]propyl}carboxamido-1,2,3,6-tetrahydropyrimidine dihydrochloride.** To 6-(benzofuran-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)carbonylpyrimidine (0.04 g, 0.085 mmol) in 10 ml of dry dichloromethane, 3-[4-(2-pyridyl)-piperidine-1-yl]propylamine (0.037 g, 0.17 mmol) was added and the solution was stirred at room temperature for 24 hours. The reaction mixture was stirred for another 1 hour after addition of 2 ml of 6N HCl. After

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neutralization with 10% aqueous KOH solution, the reaction mixture was extracted into dichloromethane (3 x 10 ml). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product
5 was purified by flash chromatography (EtOAc: MeOH, 4.5:0.5) to give 0.040 g (89%) as a syrup ; ¹H-NMR (CDCl₃): δ 1.74-2.10 (m, 7 H), 2.46 (s, 6 H), 2.70-2.72 (m, 1 H), 3.05 (d, J = 12.1 Hz, 2 H), 3.34-3.48 (m, 2 H), 3.76 (s, 3 H), 6.82 (s, 1 H), 7.11-7.32 (m, 3 H),
10 7.54-7.78 (m, 4 H), 8.53 (d, J = 4.6 Hz, 1 H), 8.89 (t, J = 5.16 Hz, 2 H).

To the free base (0.04g, 0.07 mmol) in 4 ml of dichloromethane, 5 ml of 1N HCl in ether was added, and
15 the solution concentrated under reduced pressure. Recrystallization from ether gave 0.040 g (87%) of 6-(3,4-benzofurazan-5-yl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]propyl} carboxamido-1,2,3,6-tetrahydropyrimididine
20 dihydrochloride as a white solid; m.p. 200-204 °C; Anal. Calcd. for C₂₇H₃₃Cl₂N₅O₅.2.5 H₂O: C, 49.77; H, 5.88. Found: C, 49.41; H 5.20.

Example 17

25 6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-pentyl)-2,4-dimethylpyrimidine (Scheme 9).

a. 6-(3,4-Difluorophenyl)-1,6-dihydro-2,4-dimethyl-5-methoxycarbonylpyrimidine. To a solution of acetamidine hydrochloride (1.53 g, 16.2 mmol.) in DMF (10 mL) were added a solution of potassium tert-butoxide (1.33 g, 11.8 mmol.) in DMF (10 mL) and a solution of methyl {2-(3,4-difluorophenyl) methylene}-3-oxobutanoate (2.6 g, 10.8 mmol.) in DMF (10 mL) at 0°C. After the mixture was stirred for 0.5 hour at 0°C, p-toluenesulfonic acid monohydrate (4.1 g, 21.5 mmol.)

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was added. The mixture was heated at 100-120°C for 2 hrs. The reaction mixture was cooled to room temperature, quenched with aqueous NaOH solution (2N, 60 mL), and extracted with ether. The organic layer was dried over Na₂SO₄ and evaporated. The residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 59% yield (1.8 g) as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 1.98 (3H, s), 2.31 (3H, s), 3.59 (3H, s), 5.47 (1H, s), 7.03-7.05 (3H, m).

10

b. 1-(5-Chloropentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-2,4-dimethyl-5-methoxycarbonylpyrimidine. To a suspension of NaH (90 mg, 60% dispersion in mineral oil, 2.25 mmol.) in THF (7 mL) was added a solution of the above yellow solid (0.6 g, 2.14 mmol.) in THF (8 mL) at 0°C. After 20 min, 1-bromo-5-chloropentane (1 mL, d 1.408, 7.59 mmol.) was added. The reaction mixture was then refluxed overnight. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 75% yield (0.614 g) as a yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 1.42-1.75 (6H, m), 2.17 (3H, s), 2.28 (3H, s), 3.05-3.45 (2H, m), 3.49 (2H, t, J=5.88Hz), 3.63 (3H, s), 5.23 (1H, s), 7.01-7.15 (3H, m).

25

c. 6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-pentyl)-2,4-dimethylpyrimidine. A mixture of the above yellow oil (0.667 g, 1.73 mmol.), 4-methoxycarbonyl-4-phenyl piperidine (0.76 g, 3.47 mmol.), potassium carbonate (0.96 g, 6.95 mmol.), sodium iodide (0.52 g, 3.47 mmol.) and 1,4-dioxane (15 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 80:20 v/v ethyl acetate-2M ammonia in methanol) to give the title compound in 78% yield

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(0.768 g) as a yellow oil: CIMS, m/z 568 (MH⁺); ¹H NMR (300 MHz, CDCl₃) δ 1.23-1.28 (2H, m), 1.43-1.51 (2H, m), 1.77-2.13 (8H, m), 2.16 (3H, s), 2.28 (3H, s), 2.47-2.55 (2H, m), 2.74-2.81 (2H, m), 3.00-3.12 (1H, m), 3.22-3.38 (1H, m), 3.613 (3H, s), 3.615 (3H, s), 5.22 (1H, s), 6.99-7.35 (3H, m).

Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a yellow foam: m.p. 170-176°C. Anal. Calc. for C₃₂H₃₉F₂N₃O₄·2HCl·2.3H₂O: C, 56.35; H, 6.74; N, 6.16; Found: C, 56.34; H, 6.62; N, 5.86.

Example 18

(+)-6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[3-(4-(2-pyridyl)-4-hydroxypiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydropyrimidine dihydrochloride.

A solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy) carbonylpurimidine (0.894 g, 2 mmol), 3-[4-(2-pyridyl)-4-hydroxypiperidin-1-yl]propylamine (0.517 g, 2.2 mmol) in tetrahydrofuran (100 mL) was stirred at room temperature for 24 hours. The reaction mixture was stirred for another 1 hour after addition of 2 ml of 6N HCl. Solvent was evaporated at reduced pressure and the residue was basified by treatment with 10% aqueous KOH solution, extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over potassium carbonate, and solvent evaporated. The crude product was purified by flash chromatography on silica gel (dichloromethane:MeOH:2M ammonia in MeOH, 90:8:4) to give 1.20 g (97%) as a syrup. The free base was dissolved in 20 mL anhydrous ether, cooled to 0-5 °C and treated with 10 mL of 1N HCl in ether. The white powder was filtered and dried to give 6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[3-(4-(2-pyridyl)-4-hydroxypiperidin-1-yl)propyl]}carboxamido-

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1,2,3,6-tetrahydropyrimidine dihydrochloride; m.p. 200-
206 °C; $[\alpha]_D = +91$ ($c = 1.15$ g, in 100 mL of
chloroform). Anal. Calcd. for $C_{27}H_{33}Cl_2F_2N_5O_4 \cdot 0.4CHCl_3$: C,
48.18; H, 4.92; N, 10.18. Found: C, 48.34; H, 5.01; N,
5 10.08.

Example 19

(+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-(2-hydroxypropyl)}carboxamido-5-methoxycarbonyl
10 -2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine
dihydrochloride

a) 3-[4-(2-Pyridyl)-piperidin-1-yl](2-hydroxypropyl)
phthalimide

15 A mixture of 4-(2-pyridyl)piperidine (3.25 g, 19.90 mmol) and 2,3-epoxypropylphthalimide (4.449 g, 21.89 mmol) in DMF (20 mL) was stirred and heated at 70 °C for 48 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (1000/28/14) as the eluent, to obtain the desired product as a viscous oil (6.15 g, 84%).

25 b) 3-[4-(2-Pyridyl)-piperidin-1-yl]-2-hydroxy propylamine

A mixture of 3-[4-(2-pyridyl)-piperidin-1-yl](2-hydroxypropyl)phthalimide (1.35 g, 3.68 mmol) and hydrazine (0.588 g, 18.4 mmol) in methanol (15 mL) was stirred and refluxed for 4.5 h. It was cooled, filtered, and the solid was washed with methanol (30 mL). Evaporation of solvent from the filtrate gave the product as a viscous oil (0.85 g, 98%).

35 c) (+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-(2-hydroxypropyl)}carboxamido-5-methoxycarbon yl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine

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dihydrochloride

A solution of (+)-6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy) carbonylpyrimidine (105 mg, 0.23 mmol), 5 3-[4-(2-pyridyl)piperidin-1-yl]-2-hydroxypropylamine (50 mg, 0.23 mmol) in tetrahydrofuran (20 mL) was stirred at room temperature for 24 hours. Solvent was evaporated at reduced pressure and the residue was basified by treatment with 10% aqueous KOH solution, 10 extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over potassium carbonate, and solvent evaporated. The crude product was purified by flash chromatography (dichloromethane:MeOH:2M ammonia in MeOH, 90:8:4) to give 120 mg (97%) as a 15 syrup; The HCl salt was prepared by treatment with 1N HCl in ether; m.p. 215-220 °C; $[\alpha]_D = +41$ ($c = 1.15$ g, in 100 mL of methanol). Anal. Calcd. for $C_{27}H_{33}N_5O_6F_2Cl_2 \cdot 0.8$ MeOH: C, 52.00; H, 5.68; N, 10.90. Found: C, 52.08; H, 5.70; N, 10.53.

20

Example 20 and Example 21

(+)-1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidin-1-yl)-(2-fluoro)propyl]carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine dihydrochloride

A mixture of (+)-1,2,3,6-tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-hydroxy)propyl]carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine (0.50 g, 0.92 mmol), 25 diethylaminosulfur trifluoride (DAST, 0.222 g, 1.38 mmol, 1.5 eq.), and benzene (50 mL) was stirred at 70 °C under dry argon atmosphere for 24 h. The TLC analysis of reaction mixture showed the complete disappearance of the starting material. Solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (20 g), using chloroform/methanol/2 M ammonia in methanol (500/16/8)

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as the eluent to give two products as a mixture of two diastereomers. These diastereomers were purified by chiral HPLC separation on Chiraldpak A3, 4.6 X 250 mm column, using isocratic condition (90% hexane and 10% ethanol containing 0.5% DEA). The retention time for the first product (example 26) was 12.97 minutes and for the second product (example 27) was 16.18 minutes. The combined yield of these products is (65 mg + 65 mg) 24%. The HCl salt was prepared by treatment with 1N HCl in ether; Example 20: m.p. 132-134 °C; $[\alpha]_D = +108$ ($c = 0.715$ g, in 100 mL of chloroform). Anal. Calcd. for $C_{28}H_{32}N_5O_4F_3Cl_2 \cdot 2.0 H_2O$: C, 53.38; H, 5.60; N, 11.12. Found: C, 53.28; H, 5.89; N, 10.96. Example 21: m.p. 130-132 °C; $[\alpha]_D = +100$ ($c = 0.7$ g, in 100 mL of chloroform). Anal. Calcd. for $C_{28}H_{32}N_5O_4F_3Cl_2 \cdot 1.5 H_2O$: C, 54.15; H, 5.52; N, 11.28. Found: C, 54.17; H, 5.57; N, 11.00.

Note: Examples 14 and 15 are two diastereomeric products derived from the (+)enantiomer at the pyrimidine part and the two possible enantiomeric compounds with respect to the fluoromethylene chiral center.

Example 22

(+)-5-Carboxamido-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]} carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

a) 3-(4-Cyano-4-phenylpiperidin-1-yl)propylphthalimide.
A mixture of 4-cyano-4-phenylpiperidine hydrochloride (111 g, 0.5 mol), 3-bromopropylphthalimide (135.39 g, 0.505 mol), potassium carbonate (276.42 g, 2 mol), and potassium iodide (5.4 g) in DMF (1 L) was stirred and heated at 100-110 °C for 8 h. About 80% of the solvent was evaporated at reduced pressure, the residue was diluted with dichloromethane (1 L) and washed with brine (3 X 300 mL) and dried (Na_2SO_4). Solvent was

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evaporated from the dichloromethane solution and the residue was treated with isopropanol (400 mL) and cooled. The pale yellow crystalline product formed was filtered, washed with ice-cold isopropanol and dried (168.6 g, 90%); M.p. 96-98 °C.

b) **3-(4-Cyano-4-phenylpiperidin-1-yl)propylamine.**
To a solution of 3-(4-cyano-4-phenylpiperidin-1-yl)propylphthalimide (112 g, 0.3 mol) in methanol (1.5 L), hydrazine (30 mL) was added and the mixture was stirred and refluxed for 20 h. It was cooled, the white solid formed was filtered and washed with more methanol (200 mL). Solvent was evaporated from the filtrate and residue was dried under vacuum for 4 h. Chloroform (500 mL) was added to this, stirred for 1 h and filtered. The white solid was washed with more chloroform (200 mL), the solvent was evaporated from the combined filtrates to leave the product as an oil (70 g, 96%).

c) **Benzyl 2-[(2,4-difluorophenyl)methylene]-3-oxopentanoate.** A solution of benzyl propionylacetate (157 g, 0.758 mol), 2,4-difluorobenzaldehyde (107.65 g, 0.758 mol), and piperidinium acetate (5.49 g, 38 mmol) in benzene (1 L) were stirred at room temperature for 96 h. The mixture was washed with water (2 X 100 mL), dried (magnesium sulfate) and the solvent evaporated under reduced pressure to get the product as a pale yellow syrup (251.2 g). It was used in the next step without further purification.

d) **5-(Benzylloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl)pyrimidine.**
A suspension of benzyl 2-[(2,4-difluorophenyl)methylene]-3-oxopentanoate (80.0 g, 0.241 mol), O-methylisourea hemisulfate (63.8 g, 0.362 mol, 1.5 eq.), NaHCO₃ (60.48 g, 0.72 mol) in ethanol (800 mL) was

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stirred at 60-70 °C for 20 h. After cooling to room temperature, the mixture was filtered, and the solid was washed with ethanol (200 mL). The solvent was evaporated from the combined filtrates and the residue
5 was purified by column chromatography (SiO₂, EtOAc/Hexane, 10%-30%) to get 5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl) pyrimidine as a pale yellow oil (39 g, 42%). The ¹H-NMR analysis showed it to be a mixture of amine/imine
10 tautomers and was used as is in the next step.

e) 5-(Benzylloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(2,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl] pyrimidine.
15 To a well stirred solution of 5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl) pyrimidine (22.5 g, 59.3 mmol) and 4-(N,N-dimethyl amino)pyridine (9.3 g, 75.8 mmol) in CH₂Cl₂ (200 mL) was added a powder of 4-nitrophenyl chloroformate (15.3 g, 75.8 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and then water (50 mL) was added. The pH of the aqueous layer was adjusted to 10-11 by the addition of 6 N sodium hydroxide. The dichloromethane layer was separated and dried (Na₂SO₄).
20 Solvent was evaporated in vacuo and the residue was purified by column chromatography (SiO₂, dichloromethane /hexane, 20%-50%) to give the product as a viscous oil (32.0 g, 98%).
25

f) 5-(Benzylloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(2,4-difluorophenyl)pyrimidine.
30 To a stirred solution of 5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(2,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (32 g, 58.17 mmol) in dichloromethane (200 mL) was added R-(+)-α-methylbenzylamine (9.16, 75.6 mmol) at room temperature
35

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and the stirring was continued for 12 h. The mixture was diluted with more dichloromethane (200 mL) and washed with 0.5 N NaOH solution (2 x 60 mL). The organic layer was dried over Na_2SO_4 , filtered and solvent was evaporated. The resulting mixture of diastereomers was separated by column chromatography (SiO_2 , 3% EtOAc in toluene). The first major product to elute was (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(2,4-difluorophenyl)pyrimidine (12.15 g, 38%). $[\alpha]_D = +214$ ($c = 1.5$ g in 100 mL CHCl_3); The second major product to elute was the other diastereomer and no effort was made to isolate it.

g) (+)-5-(Benzylloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl)pyrimidine.

To a stirred solution of (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(2,4-difluorophenyl)pyrimidine (11.15 g, 20.41 mmol) in toluene (250 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (4.04 g, 26.53 mmol) and the mixture was stirred at room temperature for 14 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with 3:1 EtOAc/hexane as eluent to give (+)-5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl)pyrimidine as a viscous oil (6.15 g, 78%).

h) (+)-5-(Benzylloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(2,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.

To a well stirred solution of (+)-5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl)pyrimidine (4.1 g, 10.62 mmol) and 4-(N,N-dimethylamino)pyridine (1.69 g, 13.80 mmol) in CH_2Cl_2 (200 mL) was added a powder of 4-nitrophenyl

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chloroformate (2.78 g, 13.80 mmol) at room temperature. The reaction mixture was stirred for 12 h and washed with 0.5 N NaOH solution (2 X 50 mL). The organic layer was separated and dried (Na_2SO_4). The solvent was 5 evaporated and the residue was purified by column chromatography on silica gel using dichloromethane/hexane (20%-50%) as the eluent to give (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(2,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (5.37 g, 92%) as a 10 viscous oil.

i) (+)-5-(Benzylloxycarbonyl)-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]} carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

A mixture of (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(2,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (6.50 g, 11.81 mmol) and 3-[4-cyano-4-phenylpiperidin-1-yl]propylamine (3.60 g, 15.36 mmol) in THF (500 mL) was stirred at room temperature for 18 h. It was cooled to 0 °C and 10% HCl in water (2 mL) was added and stirred for 2 h. The mixture was washed with 0.5 N aq. NaOH solution (30 mL), dried over Na_2SO_4 and the solvent evaporated. The residue was purified by column chromatography on SiO_2 , 20 using $\text{CHCl}_3/\text{MeOH}/2\text{M NH}_3$ in MeOH (100/2/1) as eluent to obtain (+)-5-(benzyloxycarbonyl)-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine as a white foamy solid 25 (7.05 g, 93%).

j) 6-(2,4-Difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid.

To a suspension of 10% Pd-C (2.1 g) in MeOH (100 mL)

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and H₂O (20 mL) was added a solution of (+)-5-(benzyloxycarbonyl)-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]} carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine (7.55 g, 11.2 mL) in methanol (100 mL) and the mixture was hydrogenated at 80 psi for 14 h. The black suspension was filtered through a pad of celite and washed thoroughly with MeOH (2.0 L) and methanol/chloroform (1:2, 200 mL). Solvent was evaporated from the combined filtrate to leave the product (+)-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid as a white solid (6.06 g, 98%). It was used in the next step without further purification.

k) (+)-5-Carboxamido-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]} carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.
A mixture of (+)-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]} carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid (6.30 g, 11.18 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.29 g, 22.36 mmol, 2 eq.), and 4-(N,N-dimethylamino)pyridine (3.41 g, 27.95 mmol, 2.5 eq) in anhydrous dichloromethane (400 mL) was stirred at room temperature for 2 h. To this, 40% aqueous ammonia (6.13 g, 5 eq) was added and the stirring was continued for 12 h. The mixture was diluted with 200 mL of dichloromethane and washed with saturated aqueous ammonium chloride solution (3 X 200 mL). Solvent was evaporated from the dried (sodium sulfate) dichloromethane solution and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (100/2/1) as the eluent, to obtain the desired product as a white

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powder (5.45 g, 87%); m.p. 210-211 °C; Part of the compound (300 mg) was dissolved in dichloromethane (3 mL), cooled to 0-5 °C and treated with 1N HCl in ether (10 mL) followed by anhydrous ether (20 mL). The white 5 powder formed was filtered, washed with ether (100 mL) and dried (320 mg, 100%); m.p. 196-97 °C; $[\alpha]_D = +126$ (c = 0.505 g, in 100 mL of 1:1 chloroform/MeOH). Anal. Calcd. for $C_{29}H_{33}N_6O_3F_2Cl$: C, 59.27; H, 5.78; N, 14.24. Found: C, 59.33; H, 5.67; N, 14.32.

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Example 23

(+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4(2-pyridyl)piperidin-1-yl)propyl]carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine dihydrochloride.

15

a) 2-Cyanoethyl 4-methoxyacetoacetate.

A mixture of methyl 4-methoxyacetoacetate (50 g, 0.342 mol) and 3-hydroxypropionitrile (31.61 g, 0.444 mol) was heated to 160-180 °C in a distillation set-up. It 20 was kept at that temperature for 2 h until the distillation of the methanol stopped. The residual yellow oil of 2-cyanoethyl 4-methoxyacetoacetate (56.4 g, 90%) was used as is without any further purification.

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b) 2-Cyanoethyl 2-[(3,4-difluorophenyl)methylene]-3-oxo-4-methoxybutyrate.

A solution of 2-cyanoethyl 4-methoxyacetoacetate (17.8 g, 0.125 mol), 3,4-difluorobenzaldehyde (25.5 g, 6.26 mmol), acetic acid (0.376 g, 6.26 mmol), and piperidine (0.533 g, 6.26 mmol) in benzene (500 mL) were added 30 molecular sieves (200 g) and the mixture was stirred at room temperature for 24 h. Then the solvent was evaporated under reduced pressure and the residue was purified by column chromatography using chloroform/ethyl acetate (100:5) to get the product as 35 an oil (29 g, 75%).

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c) 5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine.

A suspension of 2-cyanoethyl 2-[(3,4-difluorophenyl)methylene]-3-oxo-4-methoxybutyrate (29 g, 0.094 mol), O-methylisourea hemisulfate (21 g, 0.121 mol, 1.3 eq.), dimethylaminopyridine (29.67 g, 0.243 mol, 2.5 eq.) in ethanol (400 mL) was stirred at 50-55 °C for 6 h. The solvent was evaporated from the combined filtrates and the residue was purified by column chromatography (SiO₂, EtOAc/hexane, 10%-30%) to get 5-(2-cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine as a pale yellow oil (10.5 g, 31%). The ¹H-NMR analysis showed it to be a mixture of amine/imine tautomers and was used as is in the next step.

d) 5-(2-Cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.

To a well stirred solution of 5-(2-cyanoethoxy carbonyl)-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine (10.5 g, 28.74 mmol) and 4-(N,N-dimethylamino)pyridine (6.95 g, 34.49 mmol) in CH₂Cl₂ (100 mL) was added a powder of 4-nitrophenyl chloroformate (4.21 g, 34.49 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and then the solvent was evaporated. The residue was purified by column chromatography (SiO₂, dichloromethane/hexane, 20%-50%) to give the product as a viscous oil (6.5 g, 43%).

e) 5-(2-Cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine.

To a stirred solution of 5-(2-cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]

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pyrimidine (6.5 g, 12.25 mmol) in dichloromethane (150 mL) was added R-(+)- α -methylbenzylamine (1.78 g, 14.7 mmol) at room temperature and the stirring was continued for 12 h. Solvent was evaporated and the residue was purified by column chromatography (SiO₂, 10-20% EtOAc in hexane). The first major product to elute was (+)-5-(2-cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (2.54 g, 44.5%). $[\alpha]_D = +177.8$ (*c* = 9.2 g in 100 mL CHCl₃); The second major product to elute was the other diastereomer and no effort was made to isolate it.

f) (+)-5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine.

To a stirred solution of (+)-5-(2-cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (2.80 g, 5.46 mmol) in toluene (80 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.250 g, 1.64 mmol) and the mixture was stirred at 75 °C for 1 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with 3:1 EtOAc/hexane as eluent to give (+)-5-(2-cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine as a viscous oil (0.82 g, 40.5%).

g) (+)-5-(2-Cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.

To a well stirred solution of (+)-5-(2-cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine (0.82 g, 2.24 mmol) and 4-(*N,N*-dimethylamino)pyridine (0.329 g, 2.69 mmol) in CH₂Cl₂ (200 mL) was added a powder of 4-nitrophenyl chloroformate (0.543 g, 2.69 mmol) at room

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temperature. The solvent was evaporated and the residue was purified by column chromatography on silica gel using dichloromethane/hexane (20%-50%) as the eluent to give (+)-5-(2-cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.80 g, 67%) as a viscous oil.

10 h) (+)-5-(2-Cyanoethoxycarbonyl)-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

15 A mixture of (+)-5-(2-cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.44 g, 0.83 mmol) and 3-[4-(2-pyridyl)piperidin-1-yl]propylamine (0.218 g, 0.996 mmol) in THF (15 mL) was stirred at room temperature for 12 h. It was cooled to 0 °C and 10% HCl in water (2 mL) was added and stirred for 2 h. Solvent was evaporated and the residue was purified by column chromatography on SiO₂ using CHCl₃/MeOH/2M NH₃ in MeOH (100/2/1) as eluent to obtain (+)-5-(2-cyanoethoxycarbonyl)-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine as a white foamy solid (0.41 g, 83%).

30 i) 6-(3,4-Difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid.

35 To a stirred solution of (+)-5-(2-cyanoethoxycarbonyl)-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine (0.34 g, 0.57 mmol) in acetone (5 mL) at 0 °C, sodium hydroxide solution (1 N,

1.71 mL) was added drop wise and the stirring was continued until the disappearance of the starting material (1 hour). Most of the acetone from the mixture was evaporated under reduced pressure while keeping the temperature at 0 °C and the residue was adjusted to pH 7.0 by the addition of 1N hydrochloric acid. The white precipitate of 6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid formed was filtered and dried under vacuum (0.30 g, 96%).

j) (+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

A mixture of (+)-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid (0.30 g, 0.55 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.212 g, 1.1 mmol, 2 eq.), and 4-(N,N-dimethylamino)pyridine (0.134 g, 1.1 mmol, 2 eq) in anhydrous dichloromethane (20 mL) was stirred at room temperature for 2 h. To this, 40% aqueous ammonia (0.64 g, 10 eq) was added and the stirring was continued for 12 h. The mixture was diluted with 20 mL of dichloromethane and washed with saturated aqueous ammonium chloride solution (3 X 200 mL). Solvent was evaporated from the dried (sodium sulfate) dichloromethane solution and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (100/2/1) as the eluent, to obtain the desired product as a white powder (0.232 g, 78%); The HCl salt of this compound was prepared by treatment with 1 N HCl in ether. m.p.

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95-97 °C; $[\alpha]_D = +139$ ($c = 2.1$ g, in 100 mL of chloroform). Anal. Calcd. for $C_{27}H_{34}N_6O_4F_2Cl_2 \cdot 2.2 H_2O$: C, 49.50; H, 5.91; N, 12.83. Found: C, 49.50; H, 5.89; N, 12.43.

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Example 24

(+)-5-Methoxycarbonyl-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

10

A mixture of (+)-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid (0.30 g, 0.55 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.212 g, 1.1 mmol, 2 eq.), and 4-(N,N-dimethylamino)pyridine (0.134 g, 1.1 mmol, 2 eq) in methanol (20 mL) was stirred at room temperature for 20 h. Solvent was evaporated and the residue was dissolved in 20 mL of dichloromethane and washed with saturated aqueous ammonium chloride solution (3 X 200 mL). Solvent was evaporated from the dried (sodium sulfate) dichloromethane solution and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (100/2/1) as the eluent, to obtain the desired product as a white powder (278 mg, 91%); The HCl salt of this compound was prepared by treatment with 1 N HCl in ether. m.p. 180-184 °C; $[\alpha]_D = +122$ ($c = 1.25$ g, in 100 mL of methanol). Anal. Calcd. for $C_{28}H_{35}N_5O_5F_2Cl_2 \cdot 1.0 H_2O$: C, 51.86; H, 5.75; N, 10.80. Found: C, 52.14; H, 5.72; N, 10.53.

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Example 25

(+)-1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)-(2-oxo)propyl]}carboxamido-5-methoxy carbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethyl pyrimidine dihydrochloride

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a) Methyl 2-[(3,4-difluorophenyl) methylene]-3-oxo-4-methoxybutyrate.

A solution of methyl 4-methoxyacetooacetate (84.32 g, 0.577 mol), 3,4-difluorobenzaldehyde (82 g, 0.577 mmol), and piperidinium acetate (5.86 g, 0.068 mol) in benzene (1.5 L) were added molecular sieves (400 g) and the mixture was stirred at room temperature for 48 h. The molecular sieves were removed by filtration and the solvent was evaporated from the filtrate under reduced pressure. The residue was purified by column chromatography on silica gel using chloroform/ethyl acetate (100:3) to get the product as an oil (67 g, 47%).

b) 5-Methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine.

A suspension of methyl 2-[(3,4-difluorophenyl) methylene]-3-oxo-4-methoxybutyrate (7.50 g, 27.75 mmol), O-methylisourea hemisulfate (7.17 g, 41.63 mmol, 1.5 eq.), sodium bicarbonate (6.99 g, 83.25 mmol, 3 eq.) in ethanol (400 mL) was stirred at 50-55 °C for 6 h. The solvent was evaporated from the combined filtrates and the residue was purified by column chromatography (SiO₂, EtOAc/hexane, 10%-30%) to get 5-methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine as a pale yellow oil (4.3 g, 47%). The ¹H-NMR analysis showed it to be a mixture of amine/imine tautomers and was used as is in the next step.

c) 5-Methoxycarbonyl-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy) carbonyl]pyrimidine.

To a well stirred solution of 5-methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine (4.3 g, 13.18 mmol) and 4-(N,N-dimethylamino)pyridine (2.09 g, 17.13 mmol) in

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CH₂Cl₂ (100 mL) was added a powder of 4-nitrophenyl chloroformate (3.45 g, 17.13 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and the solid formed was removed by filtration. Solvent was evaporated from the filtrate and the residue was purified by column chromatography (SiO₂, dichloromethane/hexane, 20%-50%) to give the product as a viscous oil (3.85 g, 59%).

10 d) 5-Methoxycarbonyl-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine.

To a stirred solution of 5-methoxycarbonyl-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (3.82 g, 7.77 mmol) in THF (140 mL) was added R-(+)-α-methylbenzylamine (1.13 g, 9.33 mmol, 1.2 eq.) at room temperature and the stirring was continued for 12 h. Solvent was evaporated and the residue was purified by column chromatography (SiO₂, 10-20% EtOAc in hexane). The first major product to elute was (+)-5-methoxycarbonyl-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (1.74 g, 44.5%). [α]_D = +205.5 (c = 5.1 g in 100 mL CHCl₃); The second major product to elute was the other diastereomer and no effort was made to isolate it.

30 e) (+)-5-Methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine.

To a stirred solution of (+)-5-methoxycarbonyl-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (1.74 g, 3.67 mmol) in toluene (40 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.250 g, 1.64 mmol) and the mixture was stirred at 70-80 °C for 1.5 h. The solvent was evaporated and the residue was purified by

flash column chromatography on silica gel with 9:1 CHCl₃/EtOAc as eluent to give (+)-5-methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine as a viscous oil (1.11 g, 92.5%).

f) (+)-5-Methoxycarbonyl-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.

To a well stirred solution of (+)-5-methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine (1.11 g, 3.4 mmol) and 4-(N,N-dimethylamino)pyridine (0.54 g, 4.42 mmol) in CH₂Cl₂ (200 mL) was added a powder of 4-nitrophenyl chloroformate (0.891 g, 4.42 mmol) at room temperature. The solvent was evaporated and the residue was purified by column chromatography on silica gel using CHCl₃/EtOAc (20%-50%) as the eluent to give (+)-5-methoxycarbonyl-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (1.30 g, 78%) as a viscous oil. [α]_D = +262.2 (c = 2.3 g in 100 mL CHCl₃).

g) (+)-1,2,3,6-Tetrahydro-1-[N-[3-(4-(2-pyridyl)piperidine-1-yl)-(2-hydroxy)propyl]carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine.

A solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenoxy)carbonylpyrimidine (0.450 g, 0.91 mmol), 3-[4-(2-pyridyl)piperidin-1-yl]-2-hydroxypropylamine (0.280 g, 1.19 mmol) in tetrahydrofuran (100 mL) was stirred at room temperature for 24 hours. The reaction mixture was stirred for another 1 hour after addition of 2 ml of 6N HCl. Solvent was evaporated at reduced pressure and the residue was basified by treatment with 10% aqueous KOH solution, extracted with

dichloromethane (3 x 10 mL). The combined extracts were dried over potassium carbonate, and solvent evaporated. The crude product was purified by flash chromatography (dichloromethane:MeOH:2M ammonia in MeOH, 90:8:4) to give 0.514 g (98%) as a syrup.

5 h) (+)-1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-oxo)propyl]carboxamido-5-methoxy carbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethyl pyrimidine dihydrochloride

10 To a stirred solution of DMSO (0.174 g, 2.23 mmol) in dichloromethane (5 mL) at -78 °C, oxalyl chloride (0.135 g, 1.07 mmol) in dichloromethane (5 mL) was added and the mixture was stirred for 3 min. To this, a solution of (+)-1,2,3,6-tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-hydroxy)propyl]carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine (0.51 g, 0.889 mmol) in dichloromethane (5 mL) was added and the stirring was continued for 15 min. It was warmed to room temperature and added 5 mL of water. The pH of the mixture was adjusted to 10-11 by adding 1N NaOH and the dichloromethane layer was separated. The aqueous layer was extracted with more dichloromethane (3 X 10 mL). The combined dichloromethane extracts were dried (magnesium sulfate), solvents evaporated, and the residue was purified by flash chromatography (dichloromethane:MeOH:2M ammonia in MeOH, 90:8:4) to give 0.32 g (63%) of the product as a syrup. $[\alpha]_D = +122$ (c = 0.55 g in 100 mL CHCl₃); Anal. Calcd. for C₂₉H₃₃N₅O₆F₂Cl₂.2.5 H₂O: C, 48.77; H, 5.55; N, 10.16. Found: C, 48.71; H, 5.72; N, 9.87.

25 Example 26 and Example 27
30 Syn and anti isomers of (+)-1,2,3,6-tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-hydroximino)propyl]carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluoro

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phenyl)-4-methoxymethylpyrimidine dihydrochloride

A solution of (+)-1,2,3,6-tetrahydro-1-[N-[3-(4-(2-pyridyl)-piperidin-1-yl)-(2-oxo)propyl]carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine (0.14 g, 0.22 mmol), hydroxylamine hydrochloride (19.6 mg, 0.28 mmol), and sodium acetate (74.8 mg, 0.55 mmol) in methanol (5 mL) was stirred at room temperature for 24 h. Solvent was evaporated at reduced pressure, the residue was mixed with dichloromethane (30 mL) and washed with water. The dichloromethane solution was dried (sodium sulfate) and the solvent evaporated. The residue was purified by column chromatography on silica gel (chloroform:MeOH:2M ammonia in MeOH, 90:8:4). The first product to elute was Example 26, syn isomer with respect to oxime hydroxyl and piperidine (30 mg); $[\alpha]_D = +94.1$ ($c = 0.528$ g in 100 mL CHCl_3); The HCl salt was prepared by treatment with 1N HCl in ether; m.p. 90-92 °C; Anal. Calcd. for $\text{C}_{28}\text{H}_{34}\text{N}_6\text{O}_6\text{F}_2\text{Cl}_2 \cdot 1.5 \text{H}_2\text{O}$: C, 47.65; H, 5.35; N, 11.26. Found: C, 47.67; H, 5.56; N, 11.36.

The second product to elute was example 33, anti isomer with respect to oxime hydroxyl and piperidine (70 mg); $[\alpha]_D = +104$ ($c = 0.3$ g in 100 mL CHCl_3); The HCl salt was prepared by treatment with 1N HCl in ether; m.p. 103-105 °C; Anal. Calcd. for $\text{C}_{28}\text{H}_{34}\text{N}_6\text{O}_6\text{F}_2\text{Cl}_2 \cdot 2.2 \text{H}_2\text{O}$: C, 47.74; H, 5.51; N, 11.84. Found: C, 48.01; H, 5.72; N, 11.57.

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Example 28

(+)-1,2,3,6-Tetrahydro-1-[N-[3-(4-(2-pyridyl)-piperidin-1-yl)-(2-methoximino)propyl]carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine dihydrochloride

A solution of (+)-1,2,3,6-tetrahydro-1-[N-[3-(4-(2-pyridyl)-piperidin-1-yl)-(2-oxo)propyl]carbox

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amido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine (30 mg, 0.047 mmol), O-methoxylamine hydrochloride (7.78 mg, 0.093 mmol), and sodium acetate (32 mg, 0.24 mmol) in methanol (5 mL) was stirred at room temperature for 24 h. Solvent was evaporated at reduced pressure, the residue was mixed with dichloromethane (30 mL) and washed with water. The dichloromethane solution was dried (sodium sulfate) and the solvent evaporated. The residue was purified by column chromatography on silica gel (chloroform:MeOH:2M ammonia in MeOH, 90:8:4). Only one isomeric product was detected by this purification (20 mg, 71%); $[\alpha]_D = +98$ ($c = 0.4$ g in 100 mL CHCl_3); The HCl salt was prepared by treatment with 1N HCl in ether; m.p. 109-112 °C; Anal. Calcd. for $\text{C}_{29}\text{H}_{36}\text{N}_6\text{O}_6\text{F}_2\text{Cl}_2 \cdot 2.3\text{H}_2\text{O}$: C, 46.93; H, 5.55; N, 11.15. Found: C, 47.08; H, 5.66; N, 10.88.

Example 29

(\pm) - 1, 2, 3, 6 - Tetrahydro - 1 - { N - [3 - (4 - (2 - carboxamidophenyl) - piperazin - 1 - yl) - propyl] } carb oxamido - 5 - acetyl - 2 - oxo - 6 - (3, 4, 5 - trifluorophenyl) - 4 - methylpyrimidine dihydrochloride

a) 3 - { (3, 4, 5 - Trifluorophenyl) methylene } - 2, 4 - pentanedione.

A mixture of 3, 4, 5 - trifluorobenzaldehyde (4.2 g, 26.2 mmol), 2, 4 - pentanedione (2.62 g, 26.2 mmol), piperidine (0.430 g, 5 mmol) in benzene (150 mL) was stirred and refluxed with a Dean-Stark trap for 8 hours. Benzene was evaporated, the yellow oily residue, 2 - { (3, 4, 5 - trifluorophenyl) methylene } - 2, 4 - pentanedione, was used in the next step without any further purification.

b) 6 - (3, 4, 5 - Trifluorophenyl) - 1, 6 - dihydro - 2 - methoxy - 5 - acetyl - 4 - methylpyrimidine.

A mixture of 2 - { (3, 4, 5 - trifluorophenyl) methylene } - 2, 4 -

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pentanedione (26.2 mmol), O-methylisourea hydrogen sulfate (3.22 g, 39.3 mmol), and NaHCO₃ (6.6 g, 78.6 mmol) in EtOH (400 mL) was stirred and heated at 95-100 °C for 6 hours. The mixture was filtered, the solid residue was washed with ethanol (100 mL). Solvent was evaporated from the combined filtrate and the crude product was purified by flash column chromatography on silica gel using 10% through 25% EtOAc in hexane as the gradient eluent, to leave the product as an oil (2.80 g, 36%).

c) 6-(3,4,5-Trifluorophenyl)-1,6-dihydro-2-methoxy-5-acetyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine
To a solution of 6-(3,4,5-trifluorophenyl)-1,6-dihydro-2-methoxy-5-acetyl-4-methylpyrimidine (2.8 g, 9.38 mmol) and pyridine (10 mL) in CH₂Cl₂ (200 mL) at 0-5 °C, 4-nitrophenyl chloroformate (1.886 g, 9.38 mmol) was added and the mixture was allowed to warm to room temperature. After 12 hours solvent was evaporated and the residue was purified by flash column chromatography (SiO₂, dichloromethane/EtOAc, 10%-15%) to obtain the product as a white powder (4.0 g, 92%).

d) 6-(3,4,5-Trifluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-acetyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.
To a well-stirred solution of 6-(3,4,5-trifluorophenyl)-1,6-dihydro-2-methoxy-5-acetyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (4.0 g, 8.63 mmol) in THF (100 mL) at 0-5 °C, 6N aqueous HCl (4 mL) was added and the mixture was allowed to warm to room temperature. After 2 h, solvent was evaporated and the product dried under vacuum. The product was obtained as a pure single component and no need for further purification (3.88 g, 100%).

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e) (+)-1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-carboxamidophenyl)-piperazin-1-yl)-propyl]carboxamido-5-acetyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methylpyrimidine dihydrochloride

5 A mixture of 6-(3,4,5-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-acetyl-4-methyl-1-[(4-nitrophenoxy)carbonyl]pyrimidine (44.9 mg, 0.1 mmol) and 3-[4-(2-carboxamidophenyl)-piperazin-1-yl]-propylamine (26.2 mg, 0.1 mmol) in THF (10 mL) was stirred at room
10 temperature for 10 h and the solvent evaporated. It was redissolved in dichloromethane (10 mL), washed with ice-cold 0.5 N NaOH (2 X 5 mL), dried and solvent evaporated. The residue was purified by preparative thin layer chromatography on silica gel using
15 chloroform-methanol-2M ammonia in methanol (100/2/1) as the eluent to afford the product as a white powder (60 mg, 93%); The HCl salt was prepared by treatment with 1N HCl in ether to give the product as a dihydrochloride salt. Anal. Calcd. for C₂₈H₃₃N₆O₄Cl₂F₃0.4H₂O: C, 51.52; H, 5.22; N, 12.88. Found: C, 51.70; H, 5.25; N, 12.53.

Example 30

25 1,2,3,6-Tetrahydro-1-{N-[3-(4-(4-fluorobenzoyl)piperidin-1-yl)ethyl]carboxamido-5-methoxycarbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride

a) 6-(3,4-Difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)carbonylpyrimidine.

30 A well stirred solution of 6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)carbonylpyrimidine (10 g) in THF (200 mL) at room temperature, aqueous 6N hydrochloric acid (10 mL) was added and the stirring was continued for 3 h.

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Solvent was evaporated and the residue was dried under vacuum to obtain the product as a white powder (9.7 g, 100%); m.p. 185-186 °C.

- 5 b) 6-(3,4-Difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(2-bromoethylamino carbonyl)pyrimidine.

A mixture of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy) carbonylpyrimidine (0.5 g, 1.118 mmol), 2-bromoethylamine hydrobromide (0.458 g, 2.237 mmol), and potassium carbonate (2.0 g) in THF/water (50 mL/5 mL) were stirred at room temperature for 1h. Then most of the solvent was evaporated at reduced pressure. The residue was partitioned between dichloromethane and water (100 mL and 100 mL). The dichloromethane layer was separated, washed with ice-cold 0.5 N NaOH (2 X 50 mL) and dried (sodium sulfate). Evaporation of the solvent gave the product as a single product (0.48 g, 100%) as a white powder; m.p. 159-160 °C.

- c) 1,2,3,6-Tetrahydro-1-{N-[2-(4-(4-fluorobenzoyl)piperidin-1-yl)ethyl]carboxamido}-5-methoxycarbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride

A mixture of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(2-bromoethylamino carbonyl)pyrimidine (43 mg, 0.1 mmol), 4-(4-fluorobenzoyl)piperidine p-toluene sulfonate (57 mg, 0.15 mmol), potassium carbonate (300 mg), and potassium iodide (30 mg) in THF(10 mL) was stirred at room temperature for 20 h. The solid material was removed by filtration, the solvent from the filtrate was evaporated, and the residue was purified by preparative thin layer chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (100/2/1) as

the eluent to afford the product as a viscous oil which was converted to the HCl salt by treatment with 1N HCl in ether; m.p. 159-160 °C; Anal. Calcd. for C₂₉H₂₉N₄O₅F₃.1HCl.0.8Et₂O: C, 57.27; H, 5.85; N, 8.56. 5 Found: C, 57.31; H, 5.75; N, 8.79.

Example 31

1,2,3,6-Tetrahydro-1-{N-[3-(4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl)propyl]carboxamido-5-methoxycarbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride

a) 6-(3,4-Difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(3-bromopropylamino carbonyl)pyrimidine.

A mixture of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy) carbonylpyrimidine (1.0 g, 2.237 mmol), 3-bromopropylamine hydrobromide (0.979 g, 4.474 mmol), and potassium carbonate (4.0 g) in THF/water (100 mL/10 mL) were stirred at room temperature for 1h. Then most of the solvent was evaporated at reduced pressure. The residue was partitioned between dichloromethane and water (100 mL and 100 mL). The dichloromethane layer was separated, washed with ice-cold 0.5 N NaOH (2 X 50 mL) and dried (sodium sulfate). Evaporation of the solvent gave the product as a single product (0.98 g, 100%) as a white powder and confirmed by ¹H-NMR.

b) 1,2,3,6-Tetrahydro-1-{N-[3-(4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl)propyl]carboxamido-5-methoxycarbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride

A mixture of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(3-bromopropylamino carbonyl)pyrimidine (44.6 mg, 0.1 mmol), 4-(4-fluorophenyl)-4-hydroxypiperidine (28.7 mg, 0.15 mmol), potassium carbonate (300 mg), and potassium iodide (30 mg) in THF(10 mL) was stirred at room temperature for

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20 h. The solid material were removed by filtration, the solvent from the filtrate was evaporated, and the residue was purified by preparative thin layer chromatography on silica gel using chloroform-methanol-
5 2M ammonia in methanol (100/2/1) as the eluent to afford the product as a viscous oil which was converted to the HCl salt by treatment with 1N HCl in ether; m.p. 160-164 °C; Anal. Calcd. for C₂₉H₂₉N₄O₅F₃.1HCl.0.8Et₂O: C, 57.27; H, 5.85; N, 8.56. Found: C, 57.31; H, 5.75; N, 10 8.79.

Example 32

a) (-)-5-(Benzylloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-methoxy-carbonyl]pyrimidine.
15

To a well stirred solution of (-)-5-(benzylloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine (0.6 g, 1.5 mmol) and 4-(N,N-dimethylamino)pyridine (0.32 g, 2.66 mmol) in CH₂Cl₂ (6 mL) was added methyl chloroformate (0.2 mL, 2.66 mmol) at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel with 3:1 Petroleum ether/EtOAC as the eluting system to obtain 0.45 g (78% 20 yield) of (-)-5-(benzylloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[methoxy-carbonyl]pyrimidine as a colorless oil.

b) (-)-1,2,3,6-Tetrahydro-4-ethyl-2-oxo-6-(3,4-difluorophenyl)-1-[methoxycarbonyl]pyrimidine-5-carboxylic acid.
30

To a solution of (-)-5-(benzylloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[methoxycarbonyl]pyrimidine (0.45 g, 1.18 mmol) in 20 mL of MeOH was added 0.05 g of 10% Pd on carbon and the resulting suspension was hydrogenated under 100 psi for 35 12 h. The catalyst was then filtered through a pad of

celite and was washed thoroughly with MeOH. All the MeOH washings were collected and the solvent was removed in vacuo to obtain 0.42 g (99% yield) of (-)-1,2,3,6-tetrahydro-4-ethyl-2-oxo-6-(3,4-difluorophenyl)-1-[methoxycarbonyl]pyrimidine-5-carboxylic acid as a white solid which was used in the next reaction without further purification.

c) (-)-1,2,3,6-Tetrahydro-5-{N-[3-(4-methoxycarbonyl)-4-phenyl-piperidin-1-yl]propyl}-carboxamido-1-methoxycarbonyl-4-ethyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

To a solution of (-)-1,2,3,6-tetrahydro-4-ethyl-2-oxo-6-(3,4-difluorophenyl)-1-[methoxycarbonyl]pyrimidine-5-carboxylic acid (1.18 mmol, 0.4 g) and 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (1.23 mmol, 0.34 g) in 20 mL CH₂Cl₂, was added 4-(N,N-dimethylamino)-pyridine (1.16 mmol, 0.15 g), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.84 mmol, 0.54 g) and the resulting solution was stirred at room temperature under argon for 2 days. The solution was then transferred into a separatory funnel, extracted with CH₂Cl₂, washed with sat. NH₄Cl solution (2 X 20 mL) and then with brine (20 mL). The organic layer was separated and dried over Na₂SO₄, filtered and the solvent was evaporated in vacuo to obtain an off-white solid. It was purified by column chromatography on silica gel with 10% MeOH in EtOAc as the solvent system to obtain (-)-1,2,3,6-tetrahydro-5-{N-[3-(4-methoxycarbonyl)-4-phenyl-piperidin-1-yl]propyl}-carboxamido-1-methoxycarbonyl-4-ethyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine as a white solid (0.55 g, 79% yield). M.P. 53-55°C; [α]_D = -48.5 (c = 0.43, CHCl₃). It was characterized as HCl salt. Anal. Calcd. For C₃₁H₃₇N₄O₆F₂Cl_{0.4} CHCl₃: C, 55.23; H, 5.52; N, 8.20. Found: C, 55.29; H, 5.35; N, 7.99.

Example 33

(+)-1-3-{[4-(3,4-Difluorophenyl)-2,5-dioxo-1,2,5,7-tetrahydro-4H-furo[3,4-d]-pyrimidine-3-carbonyl]amino}-propyl-4-phenyl-piperidine-5-carboxylic acid methyl ester.

a) (+)-6-(3,4-Difluorophenyl)-1,6-dihydro-2-oxo-5-methoxy-carbonyl-4-bromomethyl-1-[(4-nitrophenyl-oxy)carbonyl]pyrimidine.

To a well stirred solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (1.5 mmol, 0.66 g) in 5 mL of chloroform was added a solution of bromine (1.5 mmol, 0.09 mL) in 3 mL of chloroform at 0°C and the solution was allowed to attain room temperature over 1.5 h. The solvent was removed in vacuo and the residue was again dissolved in CHCl₃ (20 mL) and washed with brine. The organic layer was separated, dried over Na₂SO₄, filtered and the solvent was removed in vacuo to get 0.81 g of (+)-6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-bromomethyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine as a yellow foam. It was used in the next step without any purification.

b) (+)-4-(3,4-Difluorophenyl)-2,5-dioxo-1,2,4,5,6,7-hexahydro-cyclopentapyrimidine-3-carboxylic acid-4-nitrophenyl ester.

(+)-6-(3,4-Difluorophenyl)-1,6-dihydro-2-oxo-5-methoxy-carbonyl-4-bromomethyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (1.5 mmol, 0.81 g) was heated in oil bath for 3 h (bath temperature 130°C). The brown residue thus obtained was washed with CHCl₃, and (+)-4-(3,4-difluoro-phenyl)-2,5-dioxo-1,2,4,5,6,7-hexahydro-cyclopenta pyrimidine-3-carboxylic acid-4-nitrophenyl ester was obtained as a pale brown solid which was used in the next step without further purification (crude wt. 0.51 g).

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c) (+)-1-3-[{4-(3,4-Difluorophenyl)-2,5-dioxo-1,2,5,7-tetrahydro-4H-furo[3,4-d]-pyrimidine-3-carbonyl]amino}-propyl-4-phenyl-piperidine-5-carboxylic acid methyl ester.

5 A solution of (+)-4-(3,4-difluorophenyl)-2,5-dioxo-1,2,4,5,6,7-hexahydro-cyclopenta pyrimidine-3-carboxylic acid-4-nitrophenyl ester ((0.30 mmol, 0.13 g) and 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine (0.32 mmol, 0.09 g) in 10 mL of
10 anhydrous THF was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography (CH₂Cl₂ followed by 9:1 CH₂Cl₂/MeOH) to obtain (+)-1-3-[{4-(3,4-difluorophenyl)-2,5-dioxo-1,2,5,7-tetrahydro-4H-furo[3,4-d]-pyrimidine-3-carbonyl]amino}-propyl-4-phenyl-piperidine-5-carboxylic acid methyl ester as a pale yellow solid (0.12 g, 7.0%). [α]_D = 128.1 (c = 0.525, CHCl₃). It was characterized as HCl salt. M.P. 142-145°C; Anal. Calcd. For C₂₉H₃₁N₄O₆F₂Cl₁: C, 55.55; H, 4.98; N, 8.87. Found: C, 55.25; H, 5.03; N, 8.52.

Example 34

25 (-)-1-3-[{4-(3,4-Difluorophenyl)-2,5-dioxo-1,2,5,7-tetrahydro-4H-furo[3,4-d]-pyrimidine-3-carbonyl]amino}-propyl-4-phenyl-piperidine-5-carboxylic acid methyl ester. In a similar way, (-)-1-3-[{4-(3,4-difluorophenyl)-2,5-dioxo-1,2,5,7-tetrahydro-4H-furo[3,4-d]-pyrimidine-3-carbonyl]amino}-propyl-4-phenyl-piperidine-5-carboxylic acid methyl ester was prepared starting with (-)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (overall yield 27%). M.P. 162-165 °C. [α]_D = -121.3 (c = 0.52, CHCl₃).

35

Example 35

(+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-

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carboxamidophenyl)piperazin-1yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine

a) 1-(2-Carboxamidophenyl)piperazine

5 Concentrated sulfuric acid (15 mL) was added to 1-(2-cyanophenyl)piperazine (1.5 g, 8.0 mmol) placed in a round bottom flask and the resulting slurry was stirred at room temperature for 48 h. The reaction mixture was poured on crushed ice very slowly and then basified (pH 9) with 50% solution of NaOH. The aqueous layer was extracted several times with EtOAc, dried over K_2CO_3 , filtered and the solvent was evaporated. 1-(2-carboxamidophenyl)piperazine was obtained as an off-white solid (1.2 g, 73%). It was used in the next step without further purification. Mass spectrum 206 ($M + 1$, 100%); Combustion analysis was obtained on its hydrochloride salt. Anal. Calcd. for $C_{11}H_{11}N_3OCl \cdot 0.3CHCl_3$: C, 43.23; H, 5.55; N, 13.30. Found: C, 43.58; H, 5.70; N, 12.79.

20

b) (+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-carboxamidophenyl)piperazin-1yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

25 To a solution of (+)-6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(3-bromopropylaminocarbonyl)pyrimidine (0.435 g, 1.0 mmol) and 1-(2-carboxamidophenyl)piperazine (0.4 g, 2.0 mmol) in 25 mL of anhydrous acetone was added powdered K_2CO_3 (0.69 g, 5.0 mmol) and KI (0.17 g, 1.0 mmol) and the resulting suspension was heated to reflux for 10 h. TLC indicated complete formation of the product ($R_f = 0.4$, 3:0.5 EtOAc/MeOH). The solvent was evaporated and the residue was dissolved in water (10 mL). The aqueous layer was extracted in EtOAc (3 X 30 mL), the separated organic extract was dried over Na_2SO_4 and the solvent was removed in vacuo. The residue thus obtained was purified by column chromatography on

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silica gel with EtOAc/MeOH (5:1) as the eluting system. (+)-1,2,3,6-tetrahydro-1-[N-[4-(2-carboxamido phenyl)piperazin-1yl]propyl]-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine was obtained as light yellow powder (0.48 g, 84% yield). The product was analyzed as its dihydrochloride salt. M.P. 190-193 °C; $[\alpha]_D = 98.8$ ($c = 0.31$, MeOH); Anal calcd. for $C_{28}H_{34}N_6F_2O_5Cl_2$: C, 52.16; H, 5.50; N, 12.46. Found: C, 51.84; H, 5.67; N, 12.05.

10

Example 36

1,2,3,6-Tetrahydro-1{N-[4-(N-benzimidazolyl)-piperidin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

15 To a solution of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(3-bromopropylaminocarbonyl)pyrimidine (43 mg, 0.1 mmol) in 10 mL of anhydrous acetone was added 4-(N-benzimidazolyl)-piperidine (32.6 mg, 0.15 mmol) followed by NaHCO₃ (41 mg, 0.3 mmol) and KI (16 mg, 0.1 mmol). The resulting suspension was heated to reflux for 10 h and then cooled to room temperature. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel with EtOAc followed by 10% MeOH in EtOAc to obtain 1,2,3,6-tetrahydro-1{N-[4-(N-benzimidazolyl)-piperidin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine as an oil (15 mg, 26% yield). The product thus obtained was then dissolved in 2 mL of chloroform and 0.5 mL of HCl in Et₂O (1 M) was added at room temperature. The solvent was removed in vacuo and the HCl salt was characterized by combustion analysis. M.P. 168-172 °C. Anal calcd. for $C_{29}H_{33}N_6F_2O_5Cl$: C, 50.43; H, 4.90; N, 11.86. Found: C, 50.84; H, 5.44; N, 11.46.

Example 37

(-)-6-(Benzo[1,2,5]oxadiazol-5-yl)-1-carboxamido-4-*et*

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hyl-5-[N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]carboxamido-2-oxo-1,2,3,6-tetrahydro pyrimidine.

a) 5-Methylbenzfuroxan.

5 4-Methyl-2-nitroaniline (100 g, 0.650 mol) was suspended in saturated alcoholic sodium hydroxide solution (1.50 l). To this suspension was added with cooling (5 °C) commercial aqueous sodium hypochlorite until the red color disappeared. The fluffy yellow
10 precipitate formed was filtered, washed with cold water and recrystallized from ethanol to get 5-methylbenzfuroxan (88.2 g, 89 % yield) as a pale solid.

b) 5-Methylbenzofurazan.

15 To 5-methylbenzfuroxan (88.2 g, 0.59 mol) in refluxing EtOH (75 ml) was added dropwise P(OEt)₃, (150 ml). When addition was complete, refluxing was continued for 1 more hour. The solvent was removed by rotary evaporation and the residue shaken with water (200 ml)
20 and allowed to stand overnight at (0-5°C). The brown solid so obtained was filtered, washed with water and chromatographed on silica gel to yield 5-methylbenzofurazan (70 g, 87 %) as white needles.

25 c) 5-Dibromomethylbenzofurazan.

5-Methylbenzofurazan (70 g, 0.52 mol), NBS (325 g), and benzoyl peroxide (0.5 g) were refluxed with stirring in carbon tetrachloride (1.5 l) with exclusion of moisture for 2 days. The reaction mixture was washed with water (2 X 0.5 l), brine, dried (Na₂SO₄), and the solvent removed in vacuo. The residue was chromatographed on silica (hexane/ EtOAc = 150/1) to get 122 g (80%) of the title compound as a pink solid. 5-Tribromomethylbenzofurazan (17 g, 9%) was also isolated
30 as a pink solid.
35

d) 5-Formylbenzofurazan.

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To a refluxing mixture of 5-dibromo methylbenzofurazan (122 g, 418 mmol) in EtOH (1 l) was added AgNO₃ (163 g) in 2 l of water. When addition was complete, refluxing was continued for 2 hours. The mixture was cooled and the AgBr formed was removed by filtration. The resulting solution was concentrated to a small volume and extracted with toluene (10 X 300 ml). The extract was concentrated and the residue collected was chromatographed on silica gel (3 kg), (EtOAc / hexane = 8/1000) to get the title compound (48.2 g, 78%) as a white solid.

e) 2-Cyanoethyl 3-benzo[1,2,5]oxadiazol-5-yl-2-propionyl-acrylate.
A mixture of 5-formylbenzofurazan (25.0 g, 168.8 mmol), 2-cyanoethyl 3-oxo-pentanoate (31.4 g, 203 mmol), and piperidinium acetate (1.22 g, 8.40 mmol) in benzene (1.5 l) was refluxed with a Dean-Stark trap for 24 hours. Benzene was evaporated, and the residue was chromatographed on silica (200 g) (EtOAc / CHCl₃, = 5 / 100) to get the title compound (32.36, 62.1 % yield) as a orange oil.

f) 2-Cyanoethyl 6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-1,6-dihydropyrimidine-5-carboxylate.
A mixture of 2-cyano-ethyl 3-benzo[1,2,5]oxadiazol-5-yl-2-propionyl-acrylate (19 g, 63.48 mmol), O-methylisourea hydrogen sulfate (15.3 g, 88.9 mmol), and 4-dimethylaminopyridine (21.3 g, 175 mmol) in THF (200 ml) was stirred at 65 °C for 6 hours. The solvent was evaporated and the residue was chromatographed on silica gel (~300 g) (hexane / EtOAc = 2 / 1) to get 8 g of the title compound as an orange oily solid. This reaction was repeated for many times and the yields were between 5% and 38%.

g) 6-Benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-6H-

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pyrimidine-1,5-dicarboxylic acid 5-(2-cyan-ethyl) ester
1-(4-nitro-phenyl) ester.

To a solution of 2-cyanoethyl 6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-1,6-dihydropyrimidine-5-carboxylate (3.62 g, 10.19 mmol) and 4-dimethylaminopyridine (1.49 g, 12.2 mmol) in CH₂Cl₂ (75 ml), at 0 °C, was added 4-nitrophenylchloroformate (2.46 g, 12.22 mmol). The reaction mixture was slowly warmed to r.t. at which it was stirred for 20 hours. Then, the solvent was evaporated and the residue was purified by flash column chromatography (~60 g of SiO₂, CHCl₃ / EtOAc = 100 / 3) to get the title compound (1.96 g, 37 % yield) as a yellow solid.

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h) 2-Cyanoethyl ester 6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-1-(1-phenyl- ethyl carbamoyl)-1,6-dihydro-pyrimidine-5-carboxylate.

A solution of 6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-6H-pyrimidine-1,5-dicarboxylic acid 5-(2-cyanoethyl) ester 1-(4-nitrophenyl) ester (2.2 g, 4.22 mmol) and (R)-(+)-α-methylbenzylamine (1.36 ml, 10.6 mmol) in CH₂Cl₂ (30 ml) was stirred at room temperature for 10 hours. The solvent was evaporated, and the residue was chromatographed on silica gel (100 g) (CHCl₃ / EtOAc = 30 / 1) to get the two diasteromers of the title compound (1.03 g in total, 49%).

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i) (-)-2-Cyanoethyl 6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-1,6-dihydropyrimidine-5-carboxylate.

A mixture of (-)-2-cyanoethyl ester 6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-1-(1-phenyl- ethyl carbamoyl)-1,6-dihydro-pyrimidine-5-carboxylate (557 mg, 1.11 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (82.5 ml, 0.55 mmol) in benzene (15 ml) was stirred at 50 °C for 1 hour. The solvent was evaporated, and the residue was

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chromatographed on silica gel (~30 g) (CHCl₃ / EtOAc / 2 N NH₃ in MeOH = 40 / 10 / 1) to get the title compound (270 mg, 68.5 % yield) as a yellow solid. No rotation was observed for this compound.

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j) (-)-6-Benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-6H-pyrimidine-1,5-dicarboxylic acid 5-(2-cyanoethyl) ester 1-(4-nitro-phenyl) ester.

To a solution of (-)-2-cyanoethyl 6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-1,6-dihydropyrimidine-5-carboxylate (220 mg, 0.62 mmol) and 4-dimethylaminopyridine (99 mg, 0.81 mmol) in CH₂Cl₂ (12 ml), at 0 °C, was added 4-nitrophenylchloroformate (164 mg, 0.81 mmol). The reaction mixture was slowly warmed to r.t. at which it was stirred for 24 hours. The solvent was evaporated and the residue was purified by flash column chromatography (~30 g of SiO₂, CHCl₃ / EtOAc = 38/1) to get the title compound (301 mg, 93 % yield) as a yellow solid.

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k) (-)-6-(Benzo[1,2,5]oxadiazol-5-yl)-1-carboxamido-4-ethyl-5-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}

carboxamido-2- oxo-1,6-dihydropyrimidine.

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To (-)-6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-6H-pyrimidine-1,5-dicarboxylic acid 5-(2-cyanoethyl) ester 1-(4-nitrophenyl) ester (100 mg, 0.19 mmol) in dry THF (10 ml) ammonia (gas) was introduced with a balloon at room temperature. It was stirred at room temperature for 14 hours. TLC and ¹H NMR of the reaction mixture showed that the reaction was complete. NaOH (1 N, 3 ml) was added at room temperature. After it was stirred for 6 hours, HCl solution (6 N, 4 ml) was added. It was stirred at room temperature for 14 hours. The solvent was evaporated to get a white solid which was used directly in the next step.

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A mixture of the crude product from the above step, 4-dimethyl aminopyridine (61mg, 0.5 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96 mg, 0.5 mmol) in CH₂Cl₂ (15 ml) was stirred at room temperature for 4 hours. Methyl 1-(3-amino-propyl)-4-phenyl-piperidine-4-carboxylate (140 mg, 0.5 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was chromatographed on silica gel (5 g) (CHCl₃ / MeOH / 2 N NH₃ in MeH = 250 / 2 / 1) to get the title compound as a white solid (10.8 mg, 10 % yield over 3 steps). [α]_D = -303.9. Hydrochloride of the title compound was made with HCl in ether. M.P. of the salt: 140-143 °C. Calculated for C₃₀H₃₅N₇O₆ + 1.0HCl + 0.6 ether: C, 58.03 %; H, 6.31 %; N, 14.62 %. Found: C, 58.07 %; H, 6.08 %; N, 14.66 %.

Example 38

6-(3,4-Difluoro-phenyl)-1-[3-(3',6'-dihydro-[2,4']bipyridinyl-1'-yl)-propylcarbamoyl]-4-methyl-5-methoxycarbonyl-2-oxo-1,2,3,6-tetrahydropyrimidine hydrochloride.

a) 1-(3-Aminopropyl)-4-[pyrid-2-yl]pyridinium bromide hydrobromide.

A solution of 2,4'-dipyridyl (5.0 g, 32.0 mmol) and 3-bromopropylamine hydrobromide (7.0 g, 32.0 mmol) in DMF (50.0 mL) and acetonitrile (50.0 mL) was heated at 90-95°C for 1 h. After cooling, the white solid that came out was filtered, washed with Et₂O and dried. The mother liquor was concentrated to remove Et₂O and then heated to 90-95°C for 4 h. The solvent was evaporated and the white residue was triturated with Et₂O (100.0 mL) and filtered. The combined weight of the salt was 11.6 g (97%).

b) 3-(3',6'-Dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine.

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To a solution of 1-(3-aminopropyl)-4-[pyrid-2-yl]pyridinium bromide hydrobromide (0.66 g, 1.75 mmol) in 20.0 mL MeOH was added NaBH₄ (0.101 g, 2.62 mmol) in small portions. The reaction mixture was stirred for 5 30 min and then quenched with 6M HCl solution. The solution was concentrated to 20.0 mL and basified with 50% NaOH solution to pH 12. Extracted with CHCl₃ (5 x 30.0 mL), dried over MgSO₄ and the solvent was removed to give 3-(3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-yl)-10 propylamine as an oil (0.37 g, 96% yield). It is used in the next step immediately without purification.

c) 6-(3,4-Difluoro-phenyl)-1-[3-(3',6'-dihydro-[2,4']bipyridinyl-1'-yl)-propylcarbamoyl]-4-methyl-5-methoxycarbonyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine hydrochloride.

A solution of 6-(3,4-difluorophenyl)-4-methyl-5-methoxycarbonyl-1-(4-nitrophenoxy)carbonyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine (20 mg, 0.045 mmol) and 3-(3',6'-dihydro-2'H-[2,4']bipyridyl-1-yl)propylamine (9.7 mg, 0.045 mmol) in CH₂Cl₂ (10 ml) was stirred at room temperature for 3 days. The solvent was removed in vacuum. The residue was separated on preparative TLC (CHCl₃ / MeOH = 100 / 15) 20 to get the title compound (21mg, 89 % yield) as a yellow solid. Hydrochloride salt was made with HCl in ether. M.P. of the salt: 242-244°C. Calcd for C₂₇H₂₉N₅O₄F₂ + 2.0 HCl + 1.05 CHCl₃ + 1.05 ether: C, 48.32 %; H, 5.35 %; N, 8.74 %. Found: C, 48.10 %; H, 5.13 %; N, 8.72 %.

Example 39
6-(3,4-Difluorophenyl)-1-(3-imidazol-1-yl-propylcarbamoyl)-4-methyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine-5-carboxylic acid methyl ester.

A solution of 6-(3,4-difluorophenyl)-4-methyl-5-methoxycarbonyl-1-(4-nitrophenoxy)carbonyl-2-oxo-

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1,2,3,6-tetrahydro-pyrimidine (100 mg, 0.22 mmol) and 1-(3-aminopropyl)imidazole (40 ml, 0.34 mmol) in CH₂Cl₂ (10 ml) was stirred at room temperature for 3 hours. The solvent was removed in vacuum. The residue was separated on preparative TLC (CHCl₃ / MeOH = 100 / 15) to get the title compound (80 mg, 84 % yield) as a white solid. Hydrochloride of title compound was made with HCl in ether. Calcd for C₂₀H₂₁N₅O₄F₂ + 0.3 H₂O: C, 54.74 %; H, 4.99 %; N, 15.89 %. Found: C, 54.92 %; H, 4.65 %; N, 15.77 %. M.P. of the salt: 221-224°C.

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6-(3,4-Difluorophenyl)-1-{N-[3-(2-phenylimidazol-1-yl)propyl]carboxamido-4-methyl-5-methoxycarbonyl-2-oxo-1,2,3,6-tetrahydropyrimidine hydrochloride.
A mixture of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(3-bromopropylamino carbonyl)pyrimidine (100 mg, 0.22 mmol), 2-phenylimidazole (32.3 mg, 0.22 mmol), and CsCO₃ (358 mg, 1.1 mmol) in DMF (10 ml) was stirred at room temperature for 2 days. The solid was filtered out. The solution was concentrated and separated on preparative TLC (EtOAc / hexane = 3 / 1) to get the title compound (41 mg, 37 % yield) as a white oily solid. Hydrochloride of title compound was made with HCl in ether. M.P. of the salt: 278-282 °C. Calculated for C₂₆H₂₅N₅O₄F₂ + 2.0 HCl + 0.25 H₂O: C, 52.23 %; H, 4.60 %; N, 11.60 %. Found: C, 52.21 %; H, 4.69 %; N, 11.11 %.

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Example 41 and Example 42
(+)-, and (-)-3,6-Dihydro-1-{N-[4-(2-pyridyl)-piperidine-1-yl] propyl}carboxamido-5-methoxy carbonyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methyl pyrimidine dihydrochloride.

a) Methyl 2-acetyl-3-(3,4,5-trifluoro-phenyl)-acrylate.

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A mixture of 3,4,5-trifluorobenzaldehyde (1.0 g, 6.3 mmol), methyl acetoacetate (0.81 ml, 7.5 mmol), and piperidinium acetate (45 mg, 0.31 mmol) in benzene (10 ml) was refluxed with a Dean-Stark trap for 12 hours. The solvent was evaporated, and the residue was chromatographed on silica gel (~50 g) (EtOAc / hexane = 1 / 6) to get the title compound (825 mg, 51 % yield) as a mixture of cis and trans isomers (yellow oil).

10 b) **Methyl 2-methoxy-4-methyl-6-(3,4,5-trifluorophenyl)-1,6-dihydro-pyrimidine-5-carboxylate.**

A mixture of methyl 2-acetyl-3-(3,4,5-trifluorophenyl)-acrylate (670 mg, 2.60 mmol), O-methylisourea hydrogen hemisulfate (448 mg, 3.63 mmol), and 4-dimethylaminopyridine (407 mg, 3.63 mmol) in ethanol (20 ml) was stirred at 65 °C for 2 days. The solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (30 g) (CH₂Cl₂ / EtOAc = 9 / 1) to get the title compound (390 mg, 48 % yield) as a pale yellow oil. Calculated for C₁₄H₁₃N₂O₃F₃; C, 53.50 %; H, 4.20 %; N, 8.90 %. Found: C, 53.24 %; H, 4.20 %; N, 8.60 %.

25 c) **1,6-Dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-1-(4-nitro phenoxy)carbonyl -6-(3,4,5-trifluorophenyl)-pyrimidine.**

To a solution of methyl 1,6-dihydro-2-methoxy-4-methyl-6-(3,4,5-trifluorophenyl)-pyrimidine-5-carboxylate (385 mg, 1.23 mmol) and 4-dimethylaminopyridine (195 mg, 1.60 mmol) in CH₂Cl₂ (15 ml), at room temperature, was added 4-nitrophenyl chloroformate (322 mg, 1.60 mmol). The reaction solution was stirred at room temperature for 2 days. The white solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (~20 g) (CHCl₃ / CH₃OH = 9 / 1) to get the titled compound (206 mg, 35 % yield) as a white solid. Calculated for

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$C_{21}H_{16}N_3O_2F_3$ + 1.0 H₂O: C, 50.71 %; H, 3.65 %; N, 8.45 %. Found: C, 50.83%; H, 3.29%; N, 8.33 %.

5 d) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.

A mixture of 1,6-dihydro-5-methoxycarbonyl-2-methoxy-(4-nitrophenyloxy)carbonyl-6-(3,4,5-trifluorophenyl)-4-methyl-pyrimidine (25 mg, 0.05 mmol) and 3-[4-(2-pyridyl)-piperidin-1-yl]-propylamine (16 mg, 0.078 mmol) was stirred at room temperature for 12 hours. The solvent was evaporated and the residue chromatographed on silica gel (~5 g) (CHCl₃, / EtOAc = 30 / 1) to get the title compound (16 mg, 57 % yield) as a pale solid.

20 e) 1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(3,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

25 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine from the previous step was dissolved in CH₂Cl₂ (5 ml) and concentrated HCl solution (0.5 ml) was added. The reaction mixture was stirred at room temperature for 1 hour. NaOH solution (1 N) was added to neutralized the reaction mixture. It was extracted with CH₂Cl₂. The extractant was dried (Na₂SO₄) and concentrated to get the title compound (16 mg, quantitative) as a pale solid. Hydrochloride of the title compound was made with HCl in ether. Calculated for $C_{27}H_{29}N_5O_2F_3$ + 2.0 HCl + 4.0 THF + 0.8 CH₂Cl₂: C, 54.02%; H, 6.69%; N, 7.19%. Found: C, 54.00%; H, 6.48%; N, 7.42%.

35 f) (+)-, and (-)-3,6-Dihydro-1-{N-[4-(2-pyridyl)-

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piperidine-1-yl] propyl}carboxamido-5-methoxy carbonyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methyl pyrimidine dihydrochloride.

The enantiomers were separated by chiral HPLC separation (column: chiralpak AS) of the racemic 1,2,3,6-tetrahydro-1-{N-[4-(2-pyridyl)-piperidine-1-yl]propyl}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methylpyrimidine dihydrochloride which was synthesized in the previous step. The (+) isomer: $[\alpha]_D = +80.4$ ($c = 0.2$ g in 100 ml dichloromethane); The (-) isomer: $[\alpha]_D = -82.2$. Hydrochloride salts of the title compounds was made with HCl in ether.

15 Example 43

(+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(3,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

20 a) Methyl 2-methoxyacetyl-3-(3,4,5-trifluoro-phenyl)-acrylate.

A mixture of 3,4,5-trifluoro benzaldehyde (10 g, 62.5 mmol), methyl 4-methoxyacetooacetate (9.7 ml, 75.0 mmol), and piperidinium acetate (450 mg, 3.1 mmol) in benzene (100 ml) was refluxed with a Dean-Stark trap for 8 hours. The white solid formed (some side product) was filtered out. The solvent was evaporated, and the residue was chromatographed on silica gel (~ 1 Kg) (toluene / t-butyl methyl ether = 8 / 1) to get the title compound (4.5 g, 25% yield) as a mixture of cis and trans isomers (white solid).

b) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.

35 A mixture of methyl 2-methoxyacetyl-3-(3,4,5-trifluoro-phenyl)-acrylate (6.0 g, 20.8 mmol), O-methylisourea hydrogen hemisulfate (3.6 g, 29.2 mmol),

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and 4-dimethylaminopyridine (3.6 g, 29.2 mmol) in ethanol (20 ml) was stirred at 65 °C for 12 hours. The solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (~1 kg) (hexane / ether = 2 / 1) to get the title compound (4.0 g, 56 % yield) as a pale colorless oily solid.

c) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine.

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluorophenyl)-pyrimidine (3.24 g, 9.41 mmol) and 4-dimethylaminopyridine (1.38 g, 11.3 mmol) in CH_2Cl_2 (20 ml), at room temperature, was added 4-nitrophenyl chloroformate (2.28 g, 11.3 mmol). The reaction solution was stirred at room temperature for 2 days. The white solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (hexane / ether = 1 / 1) to get the title compound (3.70 g, 77 % yield) as a yellow solid.

d) (+)-, and (-)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-[N-(2-methylbenzyl)]carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.

A mixture of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine (3.80 g, 7.46 mmol) and (R)-(+) α -methylbenzylamine (2.02 mg, 16.4 mmol) in CH₂Cl₂ was stirred at room temperature for 2 days. The solvent was evaporated and the residue chromatographed on silica gel (toluene /t-butyl methyl ether = 5 / 1) to get the title compound as yellow oil solids. For the less polar isomer (1.81 g, 50 % yield): $[\alpha]_D = +164.3$. For the more polar isomer (1.79 g, 50 % yield): $[\alpha]_D = -86.2$.

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e) (+)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.

A mixture of (+)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-[N-(2-methylbenzyl)]carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine (1.81 g, 3.81 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.28 ml, 1.90 mmol) in benzene (10 ml) was stirred at room temperature for 4 days. The solvent was evaporated, and the residue was chromatographed on silica gel (~500 g) (hexane / ether = 2.5 / 1) to get the title compound (1.2 g, 91 % yield) as a yellow oil. No rotation was observed for this compound.

f) (+)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine.

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluorophenyl)-pyrimidine (1.20 g, 3.49 mmol) and 4-dimethylaminopyridine (0.51 g, 4.18 mmol) in CH₂Cl₂ (20 ml), at room temperature, was added 4-nitrophenyl chloroformate (0.84 g, 11.3 mmol). The reaction solution was stirred at room temperature for 12 hours. The white solid formed was filtered out. Trials to purify the crude product on silica gel only hydrolyzed the desired product to the start materials. The crude product was used in the next step without any further purification.

g) (+)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.

A mixture of (+)-1,6-dihydro-2-methoxy-5-methoxy carbonyl-4-methoxymethyl-1-(4-nitrophenyloxy) carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine and 3-[4-(2-pyridyl)-piperidin-1-yl]-propylamine (215 mg,

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1.05 mmol) was stirred at room temperature for 12 hours. The solvent was evaporated and the residue chromatographed on prep. TLC ($\text{CHCl}_3 / \text{MeOH} = 100 / 15$) to get the title compound (115 mg, 22 % yield over 2 steps) as a yellow oil.

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h) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-10
10 6-(3,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

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1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine from the previous step was dissolved in CH_2Cl_2 , (5 ml) and HCl solution (6 N, 0.5 ml) was added. The reaction mixture was stirred at room temperature for 4 hour. KOH solution (1 N) was added to neutralize the reaction mixture. It was extracted with CH_2Cl_2 . The extractant was dried (Na_2SO_4) and concentrated to get the title compound (106 mg, 94 % yield) as a pale oily solid.
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 $[\alpha]_D = + 78.6$ ($c = 0.5$ g in 100 ml dichloromethane). Hydrochloride of the title compound was made with HCl in ether. Calculated for $\text{C}_{28}\text{H}_{32}\text{N}_5\text{O}_5\text{F}_3$ + 3.8 HCl+1.8 EtOAc: C, 48.44%; H, 5.80%; N, 8.02 %. Found: C, 48.19 %; H, 5.38 %; N, 8.32%.

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Example 44
(-)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(3,4,5-trifluorophenyl)-pyrimidine dihydrochloride.
a) (-)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.
35 A mixture of (-)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-[N-(2-methylbenzyl)]carbamoyl-6-(3,4,5-trifluoro-phenyl)-

pyrimidine (1.79 g, 3.80 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.28 ml, 1.90 mmol) in benzene (10 ml) was stirred at room temperature for 4 days. The solvent was evaporated, and the residue was chromatographed on silica gel (-500 g) (hexane / ether = 2.5 / 1) to get the title compound (0.92 g, 70 %) as a yellow oil. No rotation was observed for this compound.

10 b) (-)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine.

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluorophenyl)-pyrimidine (0.92 g, 2.67 mmol) and 4-dimethylaminopyridine (0.46 g, 3.74 mmol) in CH₂Cl₂ (20 ml), at room temperature, was added 4-nitrophenyl chloroformate (0.75 g, 3.74 mmol). The reaction solution was stirred at room temperature for 2 days. The white solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (hexane / ether = 3 / 1) to get the title compound (1.01 g, 79 % yield) as a yellow solid.

25 c) (-)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluorophenyl)-pyrimidine.

A mixture of (-)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine (300 mg, 0.59 mmol) and 3-[4-(2-pyridyl)-piperidin-1-yl]-propylamine (160 mg, 0.77 mmol) was stirred at room temperature for 12 hours. The solvent was evaporated and the residue chromatographed on prep. TLC (CHCl₃ / MeOH / 2 N NH₃, in MeOH = 20 / 2 / 1) to get the title compound (290 mg, 83 % yield) as a yellow oil.

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d) (-)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(3,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

5 (-)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine (290 mg, 0.49 mmol) was dissolved in CH₂Cl₂ (5 ml) and HCl solution (6 N, 2 ml) was added. The reaction mixture was stirred at room temperature for 10 hour. KOH solution (1 N) was added to neutralized the reaction mixture. It was extracted with CH₂Cl₂. The extractant was dried (Na₂SO₄) and concentrated to get the title compound (180 mg, 64 % yield) as a pale oily 10 solid. [α]_D = - 31.4 (c = 0.44 g in 100 ml dichloromethane). Hydrochloride of the title compound was made with HCl in ether. Calculated for C₂₈H₃₂N₅O₅F₃ + 2.0 HCl + 0.8 ether + 0.8 CH₂Cl₂: C, 50.59 %; H, 5.78 %; N, 9.22 %. Found: C, 50.86 %; H, 5.82 %; 15 N, 8.75 %.

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Example 45

1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(2,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

a) Methyl 2-acetyl-3-(2,4,5-trifluoro-phenyl)-acrylate. A mixture of 2,4,5-trifluorobenzaldehyde (1.0 g, 6.3 mmol), methyl acetoacetate (0.81 ml, 7.4 mmol), and piperidinium acetate (38 mg, 0.26 mmol) in benzene (10 ml) was stirred at room temperature for 2 days. The solvent was evaporated, and the residue was chromatographed on silica gel (~50 g) (hexane / ether = 5 / 1) to get the title compound (1.60 g, quantitative) as a mixture of cis and trans isomers (colorless oil).

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b) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(2,4,5-trifluoro-phenyl)-pyrimidine.

A mixture of methyl 2-acetyl-3-(2,4,5-trifluoro-phenyl)-acrylate (1.60 g, 6.20 mmol), O-methylisourea hydrogen hemisulfate (1.07 g, 8.68 mmol), and 4-dimethylaminopyridine (1.06 g, 8.68 mmol) in ethanol (10 ml) was stirred at 65 °C for 2 days. The solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (~50 g) (CH₂Cl₂ / EtOAc = 9 / 1) to get the title compound (982 mg, 50 % yield) as a pale colorless oily solid.

c) 1,6-Dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-1-(4-nitro phenoxy)carbonyl-6-(2,4,5-trifluorophenyl)-pyrimidine.

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(2,4,5-trifluoro-phenyl)-pyrimidine (600 mg, 1.91 mmol) and 4-dimethylaminopyridine (280 mg, 2.29 mmol) in CH₂Cl₂ (8 ml), at room temperature, was added 4-nitrophenyl chloroformate (462 mg, 2.29 mmol). The reaction solution was stirred at room temperature for 18 hours. The white solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (~50 g) (hexane / ether = 4 / 1) to get the title compound (143 mg, 16 % yield) as a white solid.

d) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(2,4,5-trifluoro-phenyl)-pyrimidine.

A mixture of 1,6-dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-1-(4-nitrophenoxy)carbonyl-6-(2,4,5-trifluorophenyl)-pyrimidine (70 mg, 0.146 mmol) and 3-[4-(2-pyridyl)-piperidin-1-yl]propylamine (46 mg, 0.220 mmol) was stirred at room temperature for 12 hours. The solvent was evaporated and the residue separated on preparative TLC (CHCl₃ / MeOH / 2 N NH₃ in

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MeOH = 20 / 2 / 1) to get the title compound (59 mg, 72 % yield) as a yellow oil.

e) 1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-
5 2-oxo-1-{N-[4-(2-pyridyl)- piperidine-1-yl]-propyl}carboxamido-6-(2,4,5-trifluorophenyl- pyrimidine dihydrochloride.

10 1,6-Dihydro-2-methoxy-5methoxycarbonyl-4-methyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(2,4,5-trifluoro-phenyl)-pyrimidine (59 mg, 0.11 mmol) was dissolved in THF (3 ml) and HCl solution (6 N, 2 ml) was added. The reaction mixture was stirred at room temperature for 6 hour. KOH solution (1 N) was added to neutralized the reaction mixture. It was extracted with CH₂Cl₂. The extractant was dried (Na₂SO₄) and concentrated to get the title compound (50 mg, 87 % yield) as a white solid. Hydrochloride of the title compound was made with HCl in ether. Calculated for C₂₇H₃₃N₅O₄F₂ + 2.0 HCl + 1.0 C₆H₁₂ + 1.0 CHCl₃: C, 49.68 %; H, 5.52 %; N, 8.52 %. Found: C, 49.22 %; H, 6.11 %; N, 8.59 %. M.P. of the salt: 239-243 °C.

Example 46

25 4-(3,4-Difluorophenyl)-3-[3-(3-hydroxy-3-phenyl-8-aza bicyclo[3.2.1]oct-8-yl)propylcarbamoyl]-6-methyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine-5-carboxylic acid methyl ester

a) 8-Benzyl-3-phenyl-8-azabicyclo[3.2.1]octan-3-ol:
30 N-benzyltropinone (14.4 g, 66.7 mmol) was added dropwise (neat) to a solution of phenyl magnesium bromide (100 mL, 0.1 M in THF). The addition was continued as such a rate to maintain a gentle reflux. Once the addition was complete, the reaction mixture was heated at reflux temperature for 19 hours, cooled to room temperature, poured over 200 mL of crushed ice, saturated with ammonium chloride, and extracted with 3 X 100 mL of ethyl acetate. The combined organic

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extracts were dried (K_2CO_3), solvent removed in Vacuo, and the crude product was chromatographed on 500 g of silica packed with $CHCl_3$. The column was eluted with $CHCl_3$, (1 L), 5% $EtOAc-CHCl_3$, (1 L), 10% (1 L), 20%, (1 L), 5 30% (1 L), 50% (1 L), 100% $EtOAc$ (1 L), and 10% $MeOH-EtOAc$ (2 L), to give 11.8 g (40%) of the desired product as a slightly yellow oily solid. Anal. Calc. for $C_{20}H_{23}N_1O_1$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.63; H, 8.01; N, 4.70.

10

b) 3-Phenyl-8-azabicyclo[3.2.1]octan-3-ol:

A mixture of 5.10 g of 8-benzyl-3-phenyl-8-azabicyclo [3.2.1]octan-3-ol (17.4 mmol), 3.15 g of 10% Pd/C in 50 mL of 95% ethanol was hydrogenated in a pressurized 15 bomb (200 psi) at 60-70 °C (bath temperature) for 16 hours. The reaction mixture was filtered through a pad of Celite, and the solids were washed with 5 X 30 mL of methanol. The combined organic extracts were concentrated, and the crude product was chromatographed 20 on 300 g of silica packed with $EtOAc-MeOH-isopropanol$ (30:2:1). The column was eluted with $EtOAc-MeOH-isopropanol$ 25:2:1 (1 L), 20:2:1 (1 L), and 15:2:1 (1 L) to give 3.16 g (89%) of the desired product as a slightly yellow oily solid. Anal. Calc. for $C_{13}H_{17}N_1O_1$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.57; H, 8.53; N, 6.80.

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c) 4-(3,4-Difluorophenyl)-3-[3-(3-hydroxy-3-phenyl-8-a zabicyclo[3.2.1]oct-8-yl)propylcarbamoyl]-6-methyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine-5-carboxylic acid methyl ester.

35

A mixture of 243 mg of 3-phenyl-8-azabicyclo[3.2.1] octan-3-ol (1.2 mmol), 640 mg of 1,2,3,6-tetra hydro-1-{3- bromopropyl}carboxamido-5-methoxy carbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxo pyrimidine (1.44 mmol), 197 mg of K_2CO_3 (1.44 mmol), catalytic amounts (a few crystals) of KI in 10 mL of

ethanol were heated at reflux temperature for 4 hours. The reaction mixture was cooled to room temperature, and the crude product was purified with preparative TLC (2000 microns, 10% MeOH-EtOAc) to give 290 mg (43%) of the desired product as a slightly yellow viscous oil. Anal. Calc. For $C_{30}H_{34}F_2N_4O_5$ + 1.0 Methanol: C, 61.99; H, 6.38; N, 9.33. Found: C, 62.12; H, 6.02; N, 9.58. The hydrochloride salt was prepared by dissolving 150 mg of the free base in minimum EtOAc and excess 1N HCl in ether was added. The solvent was decanted and the separated oil was triturated with ether to give the hydrochloride as a slightly yellow powder: Anal. Calc. for $C_{30}H_{34}F_2N_4O_5$ + 1.0 HCl + 1.2 H_2O : C, 57.50; H, 6.01; N, 8.94. Found: C, 57.76; H, 5.82; N, 8.50.

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Example 47 and Example 48

1,2,3,6-Tetrahydro-1-(N-(3-(3-imidazol-1-yl)propyl)amino)propylcarboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine dihydrochloride and 1,2,3,6-Tetrahydro-1-(N-(3-(2-indol-3-yl))ethyl)amino)propylcarboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine hydrochloride

In two separate reaction vessels, a mixture of 89 mg of 1,2,3,6-tetrahydro-1-{3-bromopropyl}carboxamido-5-methoxy carbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxo pyrimidine (0.200 mmol), 0.200 mmol of the following nucleophiles (25.0 mg of 1-(3-aminopropyl)imidazole, 25 mg of tryptamine), 89 mg of K_2CO_3 , in 1 mL of acetonitrile were heated at reflux temperature for 2-5 days, applied to the preparative-TLC and eluted with $CHCl_3$ -MeOH-2N NH₃ in MeOH (10:1:1) to give the title compounds. The hydrochlorides were prepared by dissolving the title compounds in minimum EtOAc, and excess 1N HCl in ether was added until no more precipitate was apparent. The solids were filtered, washed with ether, and dried under high vacuum.

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1,2,3,6-Tetrahydro-1-(N-(3-(3-imidazol-1-yl)propyl)amino)propylcarboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine dihydrochloride (12 mg): Anal. Calc. for C₂₃H₂₈F₂N₆O₄ + 2.0 HCl + 0.6 ether + 0.3 CH₂Cl₂: C, 49.31; H, 5.76; N, 13.12. Found: C, 49.07; H, 5.78; N, 13.28.

1,2,3,6-Tetrahydro-1-(N-(3-(2-indol-3-yl)ethyl)amino)propylcarboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine hydrochloride

(23 mg); Anal. Calc. for C₂₇H₂₉F₂N₅O₄ + 1.0 HCl + 3.7 THF: C, 60.58; H, 7.25; N, 8.45. Found: C, 60.84; H, 7.21; N, 8.48.

15 Example 49

6-(3,4-Difluorophenyl)-1,6-dihydro-1-methoxycarbonyl-5-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-propylaminocarbonyl)-2,4-dimethylpyrimidine

a) Benzyl 3-oxo-2-(3,4-difluorobenzylidenyl)butanoate.

20 A mixture of 3,4-difluorobenzaldehyde (7.1 g, 50 mmol.), benzyl acetoacetate (12.48 g, 65 mmol.), acetic acid (0.15 g, 2.5 mmol.), piperidine (0.212 g, 2.5 mmol.) and benzene (300 mL) was refluxed under a dean-stark trap overnight. After the removal of solvent, the residue was then dissolved in ethyl acetate and washed with saturated KHSO₄, saturated NaHCO₃, water and then dried over Na₂SO₄. The solvent was evaporated, and the residue was flash chromatographed over silica gel (eluent: 1:1 v/v ethyl acetate-hexane) to give the product in 87% yield (13.7 g) as a yellow solid.

b) 5-Benzylloxycarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-2,4-dimethylpyrimidine.

35 To a stirred solution of acetamidine hydrochloride (1.42 g, 15 mmol.) in DMF (10 mL) were added a solution of potassium tert-butoxide (1.23 g, 11 mmol.) in DMF (10mL) and a solution of the above yellow solid (3.16

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g, 10 mmol.) in DMF (10 mL) at 0°C. After the mixture was stirred for 15 min at 0°C, p-toluenesulfonic acid monohydrate (3.8 g, 20 mmol.) was added. The mixture was heated at 100-110°C for 2 hrs. After cooling, it was quenched with 2N aqueous NaOH solution and extracted with ether. The organic layer was dried over Na₂SO₄ and evaporated. The residue was flash chromatographed over silica gel (eluent: 100:5 v/v ethyl acetate-2M ammonia in methanol) to give the product in 42% yield (1.5 g) as an off-white solid.

10 c) 5-Benzylloxycarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-1-methoxycarbonyl-2,4-dimethylpyrimidine.

15 To a stirred slurry of NaH (59 mg, 60% in mineral oil, 1.47 mmol.) in THF (5 mL) was added a solution of the above off-white solid (0.5 g, 1.4 mmol.) in THF (10 mL) at 0°C. After 5 min, methyl chloroformate (0.16 g, 1.7 mmol.) was added at 0°C. Stirring was continued at room temperature for 30 min. The mixture was quenched with brine and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and evaporated to give a quantitative yield of the product as a yellow solid.

20 d) 5-Carboxy-6-(3,4-difluorophenyl)-1,6-dihydro-1-methoxycarbonyl-2,4-dimethylpyrimidine.

25 A solution of the above yellow solid (0.63 g, 1.52 mmol) in methanol (20 mL) was subjected to hydrogenation with a H₂ balloon in the presence of palladium (63 mg, 5% on C). The reaction was carried out at room temperature for 30 min. The catalyst was then filtered off and the solvent was removed in vacuo to give the product in 99% yield (0.487 g) as an off-white solid.

30 e) 6-(3,4-Difluorophenyl)-1,6-dihydro-1-methoxycarbonyl-5-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-propylaminocarbonyl)-2,4-

dimethylpyrimidine.

A mixture of the above off-white solid (0.070 g, 0.22 mmol.), 4-dimethylaminopyridine (0.040 g, 0.33 mmol.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.060 g, 0.30 mmol.) and CH₂Cl₂ (5 mL) was stirred at room temperature for 0.5 hr. After the addition of 3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine (0.075 g, 0.27 mmol.), the mixture was refluxed overnight. To the mixture was added another 25 mL of CH₂Cl₂ and washed with saturated NH₄Cl solution. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: 85:15 v/v ethyl acetate-methonal) to give the title compound in 42% yield (0.052 g) as a white solid: mp 55-57°C. Anal. Calcd. for C₃₁H₃₆F₂N₄O₅·0.5CH₂Cl₂: C, 60.52; H, 5.97; N, 8.96. Found: C, 60.61; H, 6.09; N, 8.94.

Example 50

6-(3,4-Difluorophenyl)-1,6-dihydro-5-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propylaminocarbonyl)-1-methoxymethyl-2,4-dimethylpyrimidine

a) 5-Benzoyloxycarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-1-methoxymethyl-2,4-dimethylpyrimidine.
To a stirred slurry of NaH (24 mg, 60% in mineral oil, 0.6 mmol.) in THF (5 mL) was added a solution of 5-benzoyloxycarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-2,4-dimethylpyrimidine (0.2 g, 0.56 mmol.) in THF (10 mL) at 0°C. After 10 min, chloromethyl methyl ether (0.043 mL, 0.57 mmol.) was added at 0°C. Stirring was continued at room temperature for 3 hrs. The mixture was quenched with brine and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and evaporated to give the product in 44.5% yield as a yellow oil.

b) 5-Carboxy-6-(3,4-difluorophenyl)-1,6-dihydro-1-

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methoxymethyl-2,4-dimethylpyrimidine.

A solution of the above yellow oil (0.17 g, 0.43 mmol) in methanol (20 mL) was subjected to hydrogenation with a H₂ balloon in the presence of palladium (34 mg, 5% on C). The reaction was carried out at room temperature for 0.5 hr. The catalyst was then filtered off and the solvent was removed in vacuo to give the product in 100% yield (0.13 g) as an off-white solid.

10 c) *6-(3,4-Difluorophenyl)-1,6-dihydro-5-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propylaminocarbonyl)-1-methoxymethyl-2,4-dimethylpyrimidine.*

15 A mixture of 5-carboxy-6-(3,4-difluoro-phenyl)-1,6-dihydro-1-methoxymethyl-2,4-dimethylpyrimidine (0.13 g, 0.42 mmol.), 4-dimethylaminopyridine (0.1 g, 0.84 mmol.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.16 g, 0.82 mmol.) and CH₂Cl₂ (5 mL) was stirred at room temperature for 0.5 hr. After the addition of 3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine (0.17 g, 0.62 mmol.), the mixture was refluxed overnight. To the mixture was added another 25 mL of CH₂Cl₂, and washed with saturated NH₄Cl solution. After removal of the solvent, the residue was flash chromatographed over silica gel (eluent: 80:20 v/v ethyl acetate- methanol) to give the title compound in 32% yield (0.075 g) as a pale yellow solid: mp 53-57°C. Anal. Calcd. for C₃₁H₃₈F₂N₄O₄·0.25CHCl₃: C, 62.71; H, 6.44; N, 9.36. Found: C, 62.62; H, 6.79; N, 9.19.

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Example 51

1,6-Dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pentyl)-4-methyl-6-(4-nitrophenyl)-pyrimidine

35 a) *1,6-Dihydro-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-pyrimidine.*

Sodium (0.55 g, 23.9 mmol) was allowed to react with

anhydrous EtOH (100 mL). Then the solution was cooled by an ice water bath when formamidine acetate (2.29 g, 22.0 mmol) and methyl 2-(4-nitrobenzylidenyl)acetooacetate (5.00 g, 20.1 mmol) were added. The mixture was stirred at room temperature for 3 h. The product was filtered off as a yellow powder (4.68 g, 80%). It was mixed with p-toluenesulfonic acid monohydrate (6.7 g, 35.2 mmol) in dry DMSO (125 mL) and heated at 110°C for 3 h. Ice water (450 mL) was added and the product as a tosylate was filtered off as an off-white solid (5.55 g, 78%).

b) 1-(5-Chloropentyl)-1,6-dihydro-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)pyrimidine.

The above solid (2.44 g, 5.45 mmol) was added to dry THF (50 mL) containing sodium hydride (60% oil dispersion, 480 mg, 12.0 mmol) and cooled by an ice water bath. Then 1-bromo-5-chloropentane (3 mL, 22.8 mmol) was added. The mixture was stirred at room temperature for 7 h before ice water was added. Extraction with EtOAc gave a dark oil (4.455 g) which was flash chromatographed over silica gel (120 g) eluting with EtOAc/hexane/Et₃N (15:15:1) to afford a brown oil (1.43 g, 69%).

c) 1,6-Dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenyl-piperidin-1-yl)pentyl)-4-methyl-6-(4-nitrophenyl)-pyrimidine.

The above oil (220 mg, 0.58 mmol) was mixed with 4-methoxy-carbonyl-4-phenylpiperidine (127 mg, 0.58 mmol) and potassium iodide (106 mg, 0.64 mmol) in dry glyme (4 mL) cooled by an ice water bath. Then sodium hydride (24 mg, 60% oil dispersion, 0.60 mmol) was added. The mixture was heated at reflux overnight and more KI (106 mg) was added. Reflux was continued for two more days. Ice water was added. Extraction with EtOAc (3 x 3 mL) gave a brown oil (158 mg). It was

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dissolved in CHCl₃/EtOAc and flash chromatographed over silica gel (16 g) eluting with EtOAc/MeOH/Et₃N (20:1:1) to afford a yellow oil (89 mg, 27%). Anal. Calcd. for C₃₁H₃₈N₄O₆·3/4H₂O: C, 64.62; H, 6.91; N, 9.72. Found: C, 5 64.56; H, 6.84; N, 9.76.

Example 52

6-(2,4-Difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-pentyl)-2,4-dimethyl-5-methylaminocarbonyl-pyrimidine

a) Benzyl 3-oxo-2-(2,4-difluorobenzylidene)butanoate.
A mixture of 2,4-difluorobenzaldehyde (7.1 g, 50 mmol.), benzyl acetoacetate (12.48 g, 65 mmol.), acetic acid (0.15 g, 2.5 mmol.), piperidine (0.212 g, 2.5 mmol.) and 2-propanol (300 mL) was stirred at room temperature for two days. After the removal of solvent, the residue was then dissolved in ethyl acetate and washed with saturated KHSO₄, saturated NaHCO₃, water and then dried over Na₂SO₄. The solvent was evaporated, and 15 the residue was flash chromatographed over silica gel (eluent: 1:5 v/v ethyl acetate-hexane) to give the product in 91% yield (14.3 g) as a yellow solid.

b) 5-Benzylloxycarbonyl-6-(2,4-difluorophenyl)-1,6-dihydro-2,4-dimethylpyrimidine. To a stirred solution of acetamidine hydrochloride (2.84 g, 30 mmol.) in DMF (20 mL) were added a solution of potassium tert-butoxide (2.46 g, 22 mmol.) in DMF (20mL) and a solution of the above yellow solid (6.32 g, 20 mmol.) 25 in DMF (20 mL) at 0°C. After the mixture was stirred for 15 min at 0°C, p-toluenesulfonic acid monohydrate (7.6 g, 40 mmol.) was added. The mixture was heated at 100-110°C for 2 hrs. After cooling, it was quenched with 2N aqueous NaOH solution and extracted with ether. The 30 organic layer was dried over Na₂SO₄ and evaporated. the residue was flash chromatographed over silica gel (eluent: 100:5 v/v ethyl acetate-2M ammonia in 35

Methanol) to give the product in 42% yield (1.5 g) as an off-white solid.

- c) 5-Benzylloxycarbonyl-1-(5-bromopentyl)-6-(2,4-difluorophenyl)-1,6-dihydro-2,4-dimethylpyrimidine. To a suspension of NaH (123 mg, 60% dispersion in mineral oil, 3.08 mmol.) in THF (5 mL) was added a solution of the above off-white solid (1.0 g, 2.8 mmol.) and HMPA (0.5 g, 2.8 mmol.) in THF (5 mL) at 0°C. After 15 min, 1,5-dibromopentane (1.53 mL, 11.2 mmol.) was added. The mixture was then refluxed for 30 min. The solid was filtered off. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 78% yield (1.1 g) as a yellow oil.
- d) 5-Benzylloxycarbonyl-6-(2,4-difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pentyl)-2,4-dimethyl-pyrimidine. A mixture of the above yellow oil (1.62 g, 3.2 mmol.), 4-methoxycarbonyl-4-phenyl piperidine (1.4 g, 6.4 mmol.), potassium carbonate (1.76 g, 12.7 mmol.), sodium iodide (0.45 g, 3.0 mmol.) and 1,4-dioxane (15 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 80:20 v/v ethyl acetate-2M ammonia in methanol) to give the product in 66% yield (1.36 g) as a yellow oil.
- e) 5-Carboxy-6-(2,4-difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pentyl)-2,4-dimethyl-pyrimidine. A solution of the above yellow oil (0.36 g, 0.56 mmol) in methanol (20 mL) was subjected to hydrogenation with a H₂ balloon in the presence of palladium (36 mg, 5% on C). The reaction was carried out at room temperature for 30 min. The

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catalyst was then filtered off and the solvent was removed in vacuo to give the product in quantitative yield (0.31 g) as an off-white solid.

5 f) *6-(2,4-Difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-pentyl)-2,4-dimethyl-5-methylaminocarbonyl-pyrimidine.* A mixture of the above off-white solid (0.244 g, 0.44 mmol.), 4-dimethylaminopyridine (0.26 g, 2.12 mmol.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.13 g, 0.66 mmol.) and CH₂Cl₂ (10 mL) was stirred at room temperature for 2 hrs. After the addition of methyl amine hydrogen chloride (0.089 g, 1.32 mmol.), the mixture was stirred at room temperature overnight.

10 To the mixture was added another 25 mL of CH₂Cl₂, and washed with saturated NH₄Cl solution. After removal of the solvent, the residue was flash chromatographed over silica gel (eluent: 100:20 v/v ethyl acetate-2M ammonia in methanol) to give the title compound in 22% yield (0.055 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a pale yellow solid: mp 152-155°C. Anal. Calcd. for C₃₂H₄₀F₂N₄O₃·2HCl·1.6H₂O·0.8CHCl₃: C, 51.57; H, 6.07; N, 7.33. Found: C, 51.38; H, 5.91; N, 7.27.

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Example 53

6(*R,S*)-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-4(*S*)-methyl)pentyl-2,4-dimethylpyrimidine

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a) (*S*)-(+) -3-Methylpiperidine. A mixture of (+)-mandelic acid (45.64 g, 0.3 mol) in ethyl acetate (300 mL) was heated to solution and treated with 3-methylpiperidine (29.75 g, 0.3 mol). The mixture was allowed to come to room temperature before filtration. The crystalline material was washed with 1:1 ethyl acetate-ether (400 mL). Two recrystallizations of this

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salt from ethyl acetate gave the optically pure salt in 56% yield (21.7 g).

b) (S)-(+)-N-Benzoyl-3-methylpiperidine. The above salt (21 g, 0.088 mol) was dissolved in sodium hydroxide solution (1.0 N, 200 mL). The solution was cooled to 3°C, and benzoyl chloride (12.5 g, 0.089 mol) was added dropwise over 10 min. After the addition was complete, the mixture was transferred to a separatory funnel and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated to give the pure amide in 98% yield (17.2 g): $[\alpha]_D +45.9$ (c 1.00, CH_3OH).

c) (S)-(-)-2-Methyl-1,5-dibromopentane. To the above amide powder was added phosphorus tribromide (7.81 mL, d 2.85, 0.082 mol) at 5°C over 20 min with vigorous stirring. After the addition, the mixture was warmed to room temperature, and Br_2 (4 mL, 0.082 mol) was added dropwise over 10 min. The mixture was then allowed to stand at room temperature overnight and distilled under vacuum (0.5-1 mm Hg) until the head temperature reached 80°C. The distillate was dissolved in hexane (100 mL) and washed successively with water (20 mL), concentrated sulfuric acid (4x30 mL), water (20 mL), NaOH solution (1N, 2x40 mL), and water (20 mL). The hexane solution was then dried (Na_2SO_4) and concentrated to give the product in 31% yield (6.4 g) as a light yellow liquid.

d) 1-(5-Bromo-4(S)-methylpentyl)-6(R,S)-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine. To a suspension of NaH (47mg, 60% dispersion in mineral oil, 1.17 mmol.) in THF (3 mL) was added a solution of 6-(3,4-difluoro-phenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (0.3 g, 1.07 mmol.) and HMPA (0.193 g, 1.07 mmol.) in THF (4 mL) at 0°C. After 10 min, a solution of (-)-2-methyl-

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1,5-dibromopentane (0.86 g, 3.53 mmol.) in THF (5 mL) was added. The mixture was then refluxed for 10 min. The solid formed was filtered off. After the removal of the solvent, the residue was flash chromatographed over 5 silica gel (eluent: 100:5 v/v ethyl acetate-2.0M ammonia in methanol) to give the product in 36% yield (0.169 g) as a yellow oil.

e) 6(R,S)-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-4(S)-methyl)pentyl-2,4-dimethylpyrimidine. A mixture of the above yellow oil (0.169 g, 0.38 mmol.), 4-methoxycarbonyl-4-phenyl piperidine (0.167 g, 0.76 mmol.), potassium carbonate (0.21 g, 1.52 mmol.), sodium iodide (0.057 g, 0.38 mmol.) and 1,4-dioxane (8 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 100:5 v/v ethyl acetate-2M ammonia in methanol) to give the title compound in 11% yield (0.025 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a light yellow solid: mp 155-158°C. Anal. Calcd. for C₃₃H₄₁F₂N₃O₄·2HCl·0.5H₂O: C, 59.72; H, 6.64; N, 6.33. Found: C, 59.47; H, 6.66; N, 6.10.

Example 54

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)methyl)benzyl-2,4-dimethylpyrimidine
a) 1-(3-Bromomethylbenzyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine. To a suspension of NaH (31 mg, 60% dispersion in mineral oil, 0.77 mmol.) in THF (5 mL) was added a solution of 35 6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (0.3 g, 1.07 mmol.) and HMPA

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(0.193 g, 1.07 mmol.) in THF (5 mL) at 0°C. After 15 min, α,α' -dibromo-m-xylene (0.99 g, 3.75 mmol.) was added. The mixture was then refluxed for 15 min. The solid was filtered off. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 91% yield (0.45 g) as a yellow oil.

b) 6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(3-(4-methoxycarbonyl-4-phenyl-4-phenylpiperidin-1-yl)methyl)benzyl-2,4-dimethylpyrimidine.

A mixture of the above yellow oil (0.45 g, 0.97 mmol.), 4-methoxycarbonyl-4-phenyl piperidine (0.42 g, 1.9 mmol.), potassium carbonate (0.67 g, 4.86 mmol.), sodium iodide (0.14 g, 0.97 mmol.) and 1,4-dioxane (10 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 100:5 v/v ethyl acetate-2M ammonia in methanol) to give the title compound in 17% yield (0.10 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as an off-white solid: mp 181-183°C. Anal. Calcd. for $C_{35}H_{37}F_2N_3O_4 \cdot 2HCl \cdot 1.0H_2O$: C, 60.69; H, 5.97; N, 6.07. Found: C, 60.73; H, 5.77; N, 5.94.

Example 55

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(5-(3-phenylpropylamino)pentyl)-pyrimidine

A mixture of 1-(5-bromopentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (0.186 g, 0.433 mmol.), 3-phenyl-1-propylamine (0.12 g, 0.89 mmol.), potassium carbonate (0.3 g, 2.17 mmol.), sodium iodide (70 mg, 0.46 mmol.) and 1,4-dioxane (8 mL) was refluxed overnight. The undissolved solid was

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then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 100:20:10 v/v/v CHCl₃-methanol-2M ammonia in methanol) to give the product in 54% yield (0.114 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a white solid: mp 95-97°C. Anal. Calcd. for C₂₈H₃₅F₂N₃O₂·2HCl·0.5CH₂Cl₂: C, 57.15; H, 6.39; N, 7.02. Found: C, 57.09; H, 6.65; N, 6.85.

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Example 56

(+)-6-(3,4-Difluorophenyl)-1,6-dihydro-1-(4-hydroxy-5-(4-(2-pyridyl)piperidin-1-yl)pentyl)-5-methoxycarbonyl-2,4-dimethylpyrimidine

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a) 3-Bromopropylepoxide.

To a solution of 5-bromo-1-pentene (2.15 g, 14.4 mmol.) in CH₂Cl₂ (40 mL) was added MCPBA (3.0 g, 17.3 mmol.) at 0°C slowly. After stirred at room temperature overnight, the mixture was poured into a mixture of ice and 2N NaOH solution. The separated aqueous layer was extracted with CH₂Cl₂. The combined organic layer was then washed with water, brine and dried over Na₂SO₄. The concentrated mixture was flash chromatographed over silica gel (eluent: CH₂Cl₂) to give the product in 92% yield (2.19 g) as a pale yellow liquid.

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b) 1-(4,5-Epoxyethyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine.

To a suspension of NaH (78 mg, 60% dispersion in mineral oil) in THF (10 mL) was added a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (0.5 g, 1.78 mmol.) and HMPA (0.3 mL, 1.78 mmol.) in THF (5 mL) at 0°C. After 20 min, the above pale yellow liquid (0.6 g, 3.6 mmol.) was added. The mixture was then refluxed 2hrs. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: 100:5 v/v ethyl acetate-2.0M

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ammonia in methanol) to give the product in 62% yield (0.4 g) as a yellow oil.

c) 6-(3,4-Difluorophenyl)-1,6-dihydro-1-(4-hydroxy-5-(4-(2-pyridyl)piperidin-1-ylpentyl)-5-methoxycarbonyl-2,4-dimethylpyrimidine.

A mixture of the above yellow oil (0.48 g, 1.32 mmol.), 4-(2-pyridyl)piperidine (0.32 g, 1.98 mmol.) and 1,4-dioxane (10 mL) was refluxed overnight. The concentrated mixture was then flash chromatographed over silica gel (eluent: 80:20 v/v ethyl acetate-2.0M ammonia in methanol) to give all four diastereomers in 43% yield (0.3 g). Chiral HPLC separation gave the title enantiomer which was converted to a HCl salt: $[\alpha]_D = 120.6$ (c 0.7, MeOH); mp 163-165°C. Anal. Calcd. for $C_{29}H_{36}F_2N_4O_3 \cdot 3HCl \cdot 0.7CHCl_3$: C, 49.57; H, 5.56; N, 7.79. Found: C, 49.41; H, 5.96; N, 7.38.

Example 57

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(5-(4-(2-pyridyl)piperidin-1-yl)-4-oxo)pentyl pyrimidine

To a solution of oxalyl chloride (8 mg, 0.06 mmol.) in CH_2Cl_2 (0.25 mL) was added a solution of DMSO (10 mg, 0.14 mmol.) in CH_2Cl_2 (0.3 mL) at -78°C. After 3 min, a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-1-(4-hydroxy-5-(4-(2-pyridyl)-piperidin-1-yl)pentyl)-5-methoxycarbonyl-2,4-dimethylpyrimidine (30 mg, 0.057 mmol.) in CH_2Cl_2 (1 mL) was added to the mixture which was stirred for another 15 min. The mixture was treated with triethylamine (0.04 mL) and stirred for another 5 min. Then it was allowed to warm up to room temperature. After the addition of water, it was washed with 1N NaOH and water. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (eluent: 100:20 v/v ethyl acetate-2.0M ammonia in methanol) to give the title compound in

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43% yield (13 mg) as a yellow oil. Treatment of the free base with 3 equivalents of 1M HCl in ether gave the HCl salt as a pale yellow solid: mp 135-137°C. Anal. Calcd. for $C_{29}H_{34}F_2N_4O_3 \cdot 3HCl \cdot 2H_2O \cdot 0.9CH_2Cl_2$: C, 48.11; H, 5.78; N, 7.51. Found: C, 47.99; H, 6.08; N, 7.35.

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Example 58

(+)-4-(3,4,5-Trifluorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methyl-3-(5-(4-(2-pyridyl)piperidin-1-yl)-pentyl-2(1H)-pyrimidone

10 a) 3-(5-Bromopentyl)-4-(3,4,5-trifluorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methyl-2(1H)-pyrimidone.

To a suspension of NaH (0.23 g, 60% dispersion in mineral oil, 5.8 mmol.) in THF (40 mL) was added a solution of 6-(3,4,5-trifluorophenyl-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-pyrimidine (0.6 g, 1.9 mmol.) and HMPA (0.33 mL, 1.9 mmol.) in THF (10 mL) at 0°C. After 20 min, 1,5-dibromopentane (1.75 g, 9.4 mmol.) was added. The mixture was then refluxed for 2 hrs and quenched by water. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, treated with 6N HCl (10 mL) solution and stirred at room temperature for 1 hr. It was then separated and dried over Na_2SO_4 . After the removal of solvent, the residue was flash chromatographed over silica gel (eluent: 80:20 v/v hexane-ethyl acetate) to give the product in 73% yield (0.62 g) as a yellow oil.

15 b) (+)-4-(3,4,5-Trifluorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methyl-3-(5-(4-(2-pyridyl)piperidin-1-yl)-pentyl-2(1H)-pyrimidone. A mixture of 3-(5-bromopentyl)-4-(3,4,5-trifluorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methyl-2(1H)-pyrimidone (0.3 g, 0.7 mmol.), 4-(2-pyridyl) piperidine (0.22 g, 1.4 mmol.), potassium carbonate (0.5 g, 3.6 mmol.), sodium iodide (0.1g, 0.7 mmol.) and acetone (20 mL) was refluxed overnight. The undissolved solid was then filtered off

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and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 80:20 v/v ethyl acetate-2.0M ammonia in Methanol) to give the racemic product in 85% yield (0.3 g) as a yellow oil.
5 Chiral HPLC separation afforded the title enantiomer which was converted to a HCl salt: $[\alpha]_D = 122$ (*c* 4.1, MeOH); mp 125-127°C. Anal. Calcd. for $C_{28}H_{33}F_3N_4O_3 \cdot 2HCl \cdot 2H_2O \cdot 0.2Et_2O$: C, 52.86; H, 6.32; N, 8.56. Found: C, 52.66; H, 6.37; N, 8.15.

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E x a m p l e 5 9
4-(3,4,5-Trifluorophenyl)-3,4-dihydro-5-methoxycarbon
yl-6-methyl-3-(3-(4-(2-pyridyl)piperidin-1-yl)propyl
oxycarbonyl)-2(1H)-pyrimidone.

15

a) 1-(3-Hydroxypropyl)-4-(2-pyridyl)piperidine.
A mixture of 4-(2-pyridyl)piperidine (200 mg, 1.23 mmol), 3-bromopropanol (135 mL, 1.49 mmol), potassium carbonate (620 mg, 4.49 mmol) and a catalytic amount of sodium iodide in acetone (10 mL) was heated at reflux overnight. Filtration followed by evaporation of the solvent gave a light brown oil (324 mg) which was dissolved in CHCl₃, and flash chromatographed over silica gel (20 g) eluting with EtOAc/MeOH/Et₃N (20:1:1) to afford a light brown solid (166 mg, 61%).

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b)
4-(3,4,5-Trifluorophenyl)-3,4-dihydro-5-methoxycarbon
yl-6-methyl-3-(3-(4-(2-pyridyl)piperidin-1-yl)propyl
oxycarbonyl)-2(1H)-pyrimidone.

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A mixture of 1-(3-hydroxypropyl)-4-(2-pyridyl)-piperidine (72 mg, 0.33 mmol) and 4-(3,4,5-trifluorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methyl-3-(4-nitrophenoxy carbonyl)-2(1H)-pyrimidine (152 mg, 0.33 mmol) in dry THF (8 mL) was heated at reflux overnight. The residue obtained after evaporation of the solvent was dissolved in EtOAc and flash chromatographed over silica gel (18 g) eluting with

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EtOAc/MeOH/Et₃N (100:3:3) to afford an off-white solid (133 mg, 75%). It was dissolved in CH₂Cl₂, and treated with 1M HCl in ether (0.6 mL) to give an off-white solid: mp 154°C (dec.). Anal. Calcd. for C₂₇H₂₉F₃N₄O₅·2HCl·2H₂O: C, 49.47; H, 5.38; N, 8.55. Found: C, 49.48; H, 5.16; N, 8.35.

Example 60

(+)-1,2,3,6-Tetrahydro-1-{N-[4-cyano-4-(phenyl)cyclohex-1-yl]ethyl}carboxamido-5-methoxy carbonyl-4-methoxy methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride.

a) 2-[4-Cyano-4-(phenyl)cyclohex-1-yl]ethylamine.

A mixture of 4-phenyl-4-cyanocyclohexanone (5.00 g, 25.09 mmol) and ethylenediamine (5.58) and p-toluene sulfonic acid in benzene (200 mL) were refluxed for 4 h in a Dean-Stork set-up to remove the water formed. Solvent was evaporated and the residue was redissolved in methanol and cooled to 0 °C. To this, sodium borohydride (1.5 g) was added in portions and the mixture was stirred at room temperature for 3 h. Solvent was evaporated, the residue was dissolved in dichloromethane (300 mL), washed with brine (2 X 200 mL) and dried (sodium sulfate). Solvent was evaporated and the residue was dried under vacuum to leave the product as an oil (5.2 g). The ¹H-NMR showed this product to be pure and found to contain the cis/trans isomers in the ratio of about 9:1. It was used as was in the next step.

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b) (+)-1,2,3,6-Tetrahydro-1-{N-[4-cyano-4-(phenyl)cyclohex-1-yl]ethyl}carboxamido-5-methoxycarbonyl-4-methoxy methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride.

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A solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenoxy)carbonylpurimidine (0.220 g, 0.448

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mmol), 2-[4-cyano-4-(phenyl)cyclohex-1-yl]ethylamine (0.130 g, 0.538 mmol) in tetrahydrofuran (100 mL) was stirred at room temperature for 24 hours. The reaction mixture was stirred for another 1 hour after addition of 2 mL of 6N HCl. Solvent was evaporated at reduced pressure and the residue was basified by treatment with 10% aqueous KOH solution, extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over potassium carbonate, and solvent evaporated. The crude product was purified by preparative thinlayer chromatography (dichloromethane:MeOH:2M ammonia in MeOH, 90:8:4). The two possible isomer were obtained in the order of less polar compound as the minor product and the more polar compound as the major component (yields: 16 mg minor and 160 mg major isomer). The HCl salts were obtained by treatment with 1N HCl in ether. The minor isomer HCl salt: m.p. 124-126 °C; $[\alpha]_D = +112$ ($c = 0.21$ g in 100 mL CHCl_3); Anal. Calcd. for $\text{C}_{30}\text{H}_{34}\text{N}_5\text{O}_5\text{F}_2\text{Cl} \cdot 0.5$ chloroform. 0.5 ether: C, 54.61; H, 5.57; N, 9.80. Found: C, 54.43; H, 5.29; N, 9.54. The major isomer HCl salt: m.p. 136-138 °C; $[\alpha]_D = +142$ ($c = 0.21$ g in 100 mL CHCl_3); Anal. Calcd. for $\text{C}_{30}\text{H}_{34}\text{N}_5\text{O}_5\text{F}_2\text{Cl} \cdot 0.4$ chloroform: C, 54.84; H, 5.21; N, 10.52. Found: C, 55.16; H, 5.39; N, 10.42.

General Procedure for the Preparation of 4,4-Diarylpiperidines:

A mixture of 0.5 g of 4-aryl-4-hydroxy piperidine, 3 mL of the aromatic substrate, and 1 g of aluminum chloride was stirred at room temperature for 3 days. The reaction mixture was poured over 10 mL of ice, diluted with *t*-butyl-methyl ether, the resulting hydrochloride salt was filtered, washed with water and ether, dried, and used in the next step after spectral characterization.

4-Phenyl-4-(4-thiomethoxy-phenyl)-piperidine hydrochloride:

From 4-phenyl-4-hydroxy-piperidine and thioanisole (82%), Anal. Calc. for $C_{18}H_{21}N_1S_1 + HCl + 0.2H_2O$: C, 66.83; H, 6.98; N, 4.33. Found: C, 66.71; H, 6.81; N, 4.24.

4-(4-Fluorophenyl)-4-(4-thiomethoxy-phenyl)-piperidine hydrochloride:

From 4-(4-fluoro-phenyl)-4-hydroxy-piperidine and thioanisole (59%), Anal. Calc. for $C_{18}H_{20}F_1N_1S_1 + HCl + 0.35CH_2Cl_2$: C, 60.14; H, 5.56; N, 3.90. Found: C, 59.96; H, 5.95; N, 3.81.

4-(4-Fluorophenyl)-4-(2-methoxy-5-fluoro-phenyl)-piperidine hydrochloride:

From 4-(4-fluorophenyl)-4-hydroxy-piperidine and 4-fluoroanisole (78%), Anal. Calc. for $C_{18}H_{19}N_1F_2O_1 + HCl + 0.2H_2O$: C, 62.96; H, 5.99; N, 4.08. Found: C, 62.72; H, 6.06; N, 4.06.

Bis-4-(4-Chlorophenyl)-piperidine hydrochloride:

From 4-(4-chlorophenyl)-4-hydroxy-piperidine and chlorobenzene (92%), Anal. Calc. for $C_{18}H_{17}N_1Cl_2 + HCl$: C, 59.58; H, 5.29; N, 3.90. Found: C, 59.58; H, 5.28; N, 3.90.

4-Phenyl-4-(4-Hydroxy-phenyl)-piperidine hydrochloride:

From 4-phenyl-4-hydroxy-piperidine and phenol (58%).

General Procedure for the preparation of 4,4-diaryl-N-(3-amino)-propylpiperidines:

A mixture of 4,4-diaryl piperidine hydrochloride (0.100 mmol), (3-bromopropyl)-carbamic acid tert-butyl ester (0.100 mmol), diisopropylethylamine (1 mL), and dioxane (2 mL) were heated at reflux 5 temperature for 2 days, cooled, chromatographed (silica prep-TLC plates) to give the BOC protected 4,4-diaryl-N-aminopropylpiperidine.

The BOC protected amine was dissolved in 1:1 TFA-dichloromethane, stirred for 6 hours, concentrated in 10 vacuo, and the crude product was chromatographed (silica gel prep-TLC plates) to give 4,4-diaryl-N-(3-amino)propylpiperidines which were used after spectral characterization.

15 General Procedure for the Preparation of
Dihydropyrimidinones:

Method A: Reaction of piperidines with
bromopropylcarbamoyl-dihydropyrimidinones:
A mixture of the 3-(3-bromopropylcarbamoyl)-
20 4-(3,4-difluoro-phenyl)-6-methyl-
2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid
methyl ester (45 mg, 0.1 mmol) and 0.1 mmol of 4,4-diaryl piperidine hydrochloride in a mixture of
dioxane-diisopropylethylamine (2-0.5 mL) was heated
25 at reflux temperature for 2 days, cooled, applied to
a preparative-TLC plate and eluted with MeOH-EtOAc
(2-3%) to give the dihydro-pyrimidine free base as
the product. The free base was dissolved in a
minimum of EtOAc and excess 1 N HCl in ether was
30 added. The product was filtered, washed with ether,
and dried.

Example 61:

3-[3-[(4-phenyl)-4-(4-thiomethoxy-phenyl)-piperidin-1-yl]-propyl-
35 carbamoyl]-4-(3,4-difluoro-phenyl)-2-oxo-1,2,3,4-tetr
ahydro-
pyrimidine-5-carboxylic acid methyl ester

hydrochloride.

Prepared by method A. 63% yield. Anal. Calc. for C₃₅H₃₈N₄F₂O₄S₁+HCl+0.2CHCl₃: C, 59.62; H, 5.57; N, 7.90. Found: C, 60.07; H, 6.27; N, 7.40.

5 Example 62:

3-[3-[(4-phenyl)-4-(4-thiomethoxy-phenyl)-piperidin-1-yl]-propylcarbamoyl]-4-(3,4-difluorophenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester hydrochloride.

Prepared by method A. 63% yield. Anal. Calc. for C₃₅H₃₇N₄F₃O₄S₁+HCl+ether: C, 60.26; H, 6.22; N, 7.21. Found: C, 60.46; H, 6.58; N, 7.41.

Example 63:

3-[3-[4-(4-Fluorophenyl)-4-(2-methoxy-5-methyl-phenyl)piperidin-1-yl-propylcarbamoyl]-4-(3,4-difluoro-phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester hydrochloride.

Prepared by method A. 63% yield. Anal. Calc. for C₃₅H₃₈N₄F₄O₅+HCl+H₂O: C, 58.13; H, 5.44; N, 7.75. Found: C, 57.97; H, 5.55; N, 7.31.

Example 64:

3-[3-[Bis-4-(4-Chlorophenyl)piperidin-1-yl-propylcarbamoyl]-4-(3,4-difluorophenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester hydrochloride.

Prepared by method A. 71% yield. Anal. Calc. for C₃₄H₃₄Cl₂N₄F₂O₄+HCl+ether: C, 58.35; H, 5.80; N, 7.16. Found: C, 58.23; H, 5.71; N, 7.39.

Example 65:

3-[3-[(4-phenyl)-4-(4-hydroxyphenyl)piperidin-1-yl]propyl-carbamoyl]-4-(3,4-difluorophenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester hydrochloride.

Prepared by method A. 63% yield. Anal. Calc. for C₃₄H₃₆N₄F₂O₅₁+HCl+1.4ethanol: C, 61.08; H, 6.61; N, 7.75. Found: C, 60.86; H, 6.77; N, 7.32.

Method B. Reaction of 4,4-diaryl-N-(3-aminopropyl)piperidines with p-nitrophenylcarbamoyldihydropyrimidinones:

Example 66:

3,6-Dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4,4-bis-(4-fluorophenyl)-piperidine-1-yl]-propyl}carboxamido-

6-(2,3,6-trifluorophenyl)-pyrimidine dihydrochloride.

a) Methyl 2-methoxyacetyl-3-(2,3,6-trifluorophenyl)acrylate. A mixture of 2,3,6-trifluorobenzaldehyde (5.2 g, 33 mmol), methyl 4-methoxyacetooacetate (5.7 ml, 39 mmol), and piperidinium acetate (catalytic amount) in benzene (10 ml) was stirred at room temperature for 3 days.

The solvent was evaporated, and the residue was chromatographed on silica gel (hexane/ether = 7/1) to yield the title compound (3.4 g, 36%) as a mixture of cis and trans isomers as a colorless oil.

b) 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(2,3,6-trifluorophenyl)pyrimidine.

A mixture of methyl 2-methoxyacetyl-3-(2,3,6-trifluorophenyl)-acrylate (3.4 g, 11.8 mmol), O-methylisourea hydrogen hemisulfate (2.3 g, 16.5 mmol), and 4-dimethylaminopyridine (32.0 g, 16.5 mmol) in ethanol (10 ml) was stirred at 65 °C for 24 hours, cooled and filtered. The filtrate was concentrated and chromatographed on silica gel (hexane/ether = 2/1) to yield the title compound (0.78 g, 20 % yield) as a colorless oil.

c) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(2,3,6-trifluorophenyl)-pyrimidine.

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To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(2,3,6-trifluorophenyl)-pyrimidine (0.76 g, 2.2 mmol) and 4-dimethylaminopyridine (0.33 g, 2.7 mmol) in CH₂Cl₂ (5 ml), at room temperature, was added 4-nitrophenyl chloroformate (0.54 g, 2.7 mmol). The reaction solution was stirred at room temperature for 24 hours. It was filtered. The filtrate was concentrated and chromatographed on silica gel (hexane/ether = 2/1) to give the title compound (0.98 g, 87 % yield) as a pale yellow solid.

d) 3,6-Dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4,4-bis-(4-fluorophenyl)-piperidine-1-yl]-propyl}carboxamido-6-(2,3,6-trifluorophenyl)-pyrimidine dihydrochloride.

A mixture of 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(2,3,6-trifluorophenyl)pyrimidine (25 mg, 0.05 mmol) and 3-[4,4-bis-(4-fluoro-phenyl)-piperidin-1-yl]-propylamine (20 mg, 0.06 mmol) in CH₂Cl₂ (3 ml) was stirred at room temperature for 12 hours. HCl solution (6 N, 2 ml) was added. The reaction mixture was stirred at room temperature for 6 hour. KOH solution (1 N) was added to neutralize the reaction mixture, and was extracted with CH₂Cl₂. The extracts were dried (Na₂SO₄), concentrated and the product was chromatographed on prep. TLC (CH₂Cl₂ : CH₃OH : 2 N NH₃, in CH₃OH = 40:2:1) to obtain the title compound (18 mg, 53%) as a colorless oil. The hydrochloride of the title compound was synthesized using HCl in ether. Calculated for C₃₅H₃₅N₅O₄F₅ + 2.0 HCl: C, 55.06%; H, 4.63%; N, 7.16%. Found: C, 55.34%; H, 4.91%; N, 7.38%.

35 Example 67:

3,6-Dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(4-chlorophenyl)-4-(5-fluoro-2-

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methoxy-phenyl)-piperidine-1-yl]-propyl}carboxamido-
6-(3,5-difluorophenyl)-pyrimidine dihydrochloride.

a) Methyl 2-methoxyacetyl-3-(3,5-difluoro-phenyl)-
acrylate.

5 A mixture of 3,5-difluorobenzaldehyde (10 g, 70 mmol), methyl 4-methoxyacetooacetate (11 ml, 80 mmol), and piperidinium acetate (catalytical amount) in benzene (100 ml) was stirred at room temperature for 3 days. The solvent was evaporated, and the residue
10 was chromatographed on silica gel (hexane/ether = 5/1) to give the cis and trans mixture of the title compound (3.7 g, 20% yield) as a yellow oil .

b) 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-
methoxymethyl-6-(3,5-difluoro-phenyl)-pyrimidine.

15 A mixture of methyl 2-methoxyacetyl-3-(3,5-difluoro-phenyl)-acrylate (3.74 g, 13.8 mmol), O-methylisourea hydrogen hemisulfate (2.68 g, 19.4 mmol), and 4-dimethylaminopyridine (2.37 g, 19.4 mmol) in ethanol (30 ml) was stirred at 65 °C for 2 days, cooled and filtered . The filtrate was concentrated and chromatographed on silica gel (hexane/ether = 3/1) to get the title compound (1.7 g, 38 % yield) as a yellow solid.

c) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-
25 methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,5-difluorophenyl)-pyrimidine.

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,5-difluorophenyl)pyrimidine (1.67 g, 5.10 mmol) and 4-dimethylaminopyridine (0.75 g, 6.1 mmol) in CH₂Cl₂ (10 ml), at room temperature, was added 4-nitrophenyl chloroformate (1.24 g, 6.1 mmol). The reaction solution was stirred at room temperature for 24 hours, and filtered. The filtrate was concentrated and chromatographed on silica gel (hexane/ether = 2/1) to yield the title compound (1.82 g, 72 % yield)

as a white solid.

d) 3,6-Dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-[N-(4-(4-chloro-phenyl)-4-(5-fluoro-2-methoxy-phenyl)-piperidine-1-yl)-propyl]carboxamido-6-(3,5-difluorophenyl)-pyrimidine dihydrochloride.

5 A mixture of

1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxy-methyl-1-(4-nitrophenyloxy)carbonyl-6-(3,5-difluorophenyl)pyrimidine (25 mg, 0.050 mmol) and 3-[4-(4-

10 chloro-phenyl)-4-(5-fluoro-2-methoxy-phenyl)-piperidin-1-yl]-propylamine (23 mg, 0.060 mmol) in CH₂Cl₂ (3 ml) was stirred at room temperature for 12 hours. HCl solution (6 N, 2 ml) was added. The reaction mixture was stirred at room temperature for 15 6 hour. KOH solution (1 N) was added to neutralize the reaction mixture, and extracted with CH₂Cl₂. The extracts were dried (Na₂SO₄), concentrated and chromatographed on prep. TLC (CH₂Cl₂ : CH₃OH : 2 N NH₃, in CH₃OH = 40:2:1) to give the title compound (18 mg, 20 50%) as a colorless oil. The hydrochloride of the title compound was synthesized using HCl in ether.

Anal. Calculated for C₃₆H₃₈ClN₄O₆F₃ + 1.0 HCl + 0.5 CHCl₃: C, 54.45%; H, 4.68%; N, 6.36%. Found: C, 54.04%; H, 4.91%; N, 6.91%.

25 Example 68:

(+)-1-(5-(4-Cyano-4-phenylpiperidin-1-yl)-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-(methoxycarbonyl)-4-methyl-2-pyrimidine.

a) (+)-1-(5-Bromo-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methyl-2-pyrimidone.

To a suspension of NaH (18 mg, 60% dispersion in mineral oil, 0.45 mmol.) in THF (5 mL) was added a solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-pyrimidine (0.12 g, 0.4 mmol.) and HMPA (0.07 mL, 0.4 mmol.) in THF (15 mL) at 0°C. After 20 min, 2(S)-methyl-1,5-

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dibromopentane (0.2 mg, 0.82 mmol.) was added. The reaction mixture was then refluxed for 2 h and quenched by water. It was partitioned between ethyl acetate and water. The organic layer was separated, 5 treated with 6N HCl (5 mL) solution and stirred at room temperature for 1 h. The organic layer was then separated and dried over Na₂SO₄. After the removal of solvent, the residue was flash chromatographed over silica gel (eluent: 1:1 hexane/ethyl acetate) to give 10 the product in 81% yield (0.15 g) as a yellow oil.

b) (+)-1-(5-(4-Cyano-4-phenylpiperidin-1-yl)-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-(methoxycarbonyl)-4-methyl-2-pyrimidone.

A mixture of (+)-1-(5-Bromo-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methyl-2-pyrimidone (0.138g, 0.31 mmol.), 4-cyano-4-phenylpiperidine hydrochloride (0.138 g, 0.62 mmol.), potassium carbonate (0.22 g, 1.6 mmol.), sodium iodide (47 mg, 0.31 mmol.) and dioxane (8 mL) was 15 refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was purified by flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 18% yield (0.030 g) as a yellow oil.

20 Treatment of the free base with one equivalent of 1M HCl in ether gave the HCl salt as a light yellow solid: mp 133-135°C; [α]_D = 87.4 (1.75 mg/mL, MeOH). Anal. Calc. for C₃₁H₃₆F₂N₄O₃·HCl·0.3CHCl₃: C, 60.35; H, 6.04; N, 8.99. Found: C, 60.26; H, 6.29; N, 8.67.

25 **Example 69:**

(+)-1-(5-(4-(2-Aminocarbonyl)phenylpiperazin-1-yl)-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxy-carbonyl-4-methyl-2-pyrimidone.

30 A mixture 1-(5-bromo-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methyl-2-pyrimidone (0.1g, 0.22 mmol.), 4-(2-aminocarbonylphenyl)piperazine (0.070 g, 0.34 mmol.),

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potassium carbonate (0.16 g, 1.2 mmol.), sodium iodide (33 mg, 0.22 mmol.) and dioxane (8 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was purified by flash chromatographed over silica gel (eluent: 20:1 ethyl acetate/2M ammonia in methanol) to give the product in 41% yield (0.052 g) as a yellow oil. Treatment of the free base with one equivalent of 1M HCl in ether gave the HCl salt as a pale yellow solid: mp 168-171°C; $[\alpha]_D = 83.5$ (2 mg/mL, MeOH). Anal. Calc. for $C_{30}H_{37}F_2N_5O_4 \cdot 2HCl \cdot 0.5CH_2Cl_2$: C, 53.48; H, 5.89; N, 10.22. Found: C, 53.74; H, 5.94; N, 9.99.

Example 70:

15 1-(5-(4-Cyano-4-phenyl)piperidin-1-yl)pentyl-6-(3,4-difluoro-phenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methyl-pyrimidine.

a) 6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxy-methyl-4-methylpyrimidine.

20 To a solution of 2-methoxyacetamidine hydrochloride (1.4 g, 11.2 mmol.) in DMF (6 mL) were added a solution of potassium tert-butoxide (0.69 g, 6.1 mmol.) in DMF (6 mL) and a solution of methyl {2-(3,4-difluorophenyl) methylene}-3-oxobutanoate (1.4 g, 5.8 mmol.) in DMF (6 mL) at 0°C. After the mixture was stirred for 0.5 hr at 0°C, p-toluenesulfonic acid monohydrate (2.2 g, 11.6 mmol.) was added. The mixture was heated at 100-120°C for 2.5 hrs. The mixture was cooled to room temperature, quenched with aqueous NaOH solution (2N, 30 mL), and extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated. The residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 44% yield (0.8 g) as a yellow oil.

35 b) 1-(5-Bromopentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine.

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- To a suspension of NaH (0.11 g, 60% dispersion in mineral oil, 2.8 mmol.) in THF (20 mL) was added a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (0.8 g, 2.6 mmol.) in THF (5 mL) at 0°C. After 20 min, 1,5-dibromopentane (0.7 mL, 5.2 mmol.) was added. The mixture was then refluxed overnight. After the removal of solvent, the residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in quantitative yield (1.2 g) as a yellow oil.
- c) 1-(5-(4-Cyano-4-phenyl)piperidin-1-yl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine.
- A mixture of 1-(5-bromopentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (0.15 g, 0.33 mmol.), 4-cyano-4-phenylpiperidine hydrochloride (0.15 g, 0.67 mmol.), potassium carbonate (0.23 g, 1.7 mmol.), sodium iodide (50 mg, 0.33 mmol.) and acetone (6 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 10:1 ethyl acetate/2M ammonia in methanol) to give the title compound in 44% yield (0.080 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as an off-white solid: mp 98-101°C. Anal. Calc. for C₃₂H₃₈F₂N₄O₃·2HCl·1.1CHCl₃: C, 51.70; H, 5.39; N, 7.29. Found: C, 51.56; H, 5.52; N, 7.27.
- Example 71:**
- (+)-6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(4(S)-methyl-5-(4-(2-methylphenyl)-4-(4-methyl-phenyl)piperidin-1-yl)pentyl)pyrimidine.
- a) (+)-1-(5-Bromo-4(S)-methylpentyl)-6-(3,4-

difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine.

To a suspension of NaH (47 mg, 60% dispersion in mineral oil, 1.17 mmol.) in THF (3 mL) was added a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-pyrimidine (0.3 g, 1.07 mmol.) and HMPA (0.193 g, 1.07 mmol.) in THF (4 mL) at 0°C. After 10 min, a solution of (-)-2-methyl-1,5-dibromopentane (0.86 g, 3.53 mmol.) in THF (5 mL) was added. The reaction mixture was then refluxed for 10 min. The solid formed was filtered off. After the removal of solvent, the residue was flash chromatographed over silica gel (eluent: 20:1 ethyl acetate/2M ammonia in methanol) to give the product in 36% yield (0.169 g) as a yellow oil. Chiral HPLC separation of the above diastereomers (Column: Chiralcel OD 20 x 250 mm. Eluent: 2-propanol/hexane/diethylamine 10:90:0.1) gave the desired enantiomer: $[\alpha]_D = 200.9$ (25.5 mg/mL, CH_2Cl_2).
b) (+)-6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(4(S)-methyl-5-(4-(2-methylphenyl)-4-(4-methyl-phenyl)piperidin-1-yl)pentyl)pyrimidine.
A mixture of (+)-1-(5-bromo-4(S)-methylpentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-pyrimidine (0.1 g, 0.23 mmol.), 4-(2-methylphenyl)-4-(4-methylphenyl)piperidine hydrochloride (0.08 g, 0.26 mmol.), potassium carbonate (0.18 g, 1.3 mmol.), sodium iodide (0.033 g, 0.26 mmol.) and acetone (8 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 10:1 ethyl acetate/2M ammonia in methanol) to give the title compound in 64% yield (0.090 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a light

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yellow solid: mp 130-133°C; $[\alpha]_D = 62.4$ (1.85 mg/mL, MeOH). Anal. Calc. for $C_{39}H_{47}F_2N_3O_2 \cdot 2HCl \cdot 2H_2O \cdot 0.65CHCl_3$: C, 58.48; H, 6.64; N, 5.16. Found: C, 58.27; H, 6.46; N, 5.40.

5 Example 72:

(+) -6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methyl-1-(5-(4-(2-methylphenyl)-4-(4-methyl-phenyl)piperidin-1-yl)pentyl)pyrimidine.

- 10 a) (+)-1-(5-Bromopentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine.

To a suspension of NaH (0.11 g, 60% dispersion in mineral oil, 2.8 mmol.) in THF (20 mL) was added a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (0.8 g, 2.6 mmol.) in THF (5 mL) at 0°C. After 20 min., 1,5-dibromopentane (0.7 mL, 5.2 mmol.) was added. The mixture was then refluxed overnight. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in quantitative yield (1.2 g) as a yellow oil. Chiral HPLC separation (Column: Chiralcel OD 20 x 250 mm. Eluent: 2-propanol/hexane/diethylamine 10:90:0.1) gave the title enantiomer: $[\alpha]_D = 190.5$ (55 mg/mL, CH_2Cl_2).
b) (+)-6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methyl-1-(5-(4-(2-methylphenyl)-4-(4-methyl-phenyl)piperidin-1-yl)pentyl)pyrimidine.

A mixture of (+)-1-(5-bromopentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (0.08 g, 0.17 mmol.), 4-(2-methylphenyl)-4-(4-methylphenyl)piperidine hydrochloride (0.063 g, 0.21 mmol.), potassium carbonate (0.14 g, 1.0 mmol.), sodium iodide (26 mg, 0.17 mmol.) and acetone (6 mL)

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was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 10:1 ethyl acetate/2M ammonia in methanol) to give the title compound in 89% yield (0.1 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a pale yellow solid: mp 137-140°C; $[\alpha]_D = 56.5$ (1.65 mg/mL, MeOH). Anal. Calc. for C₃₉H₄₇F₂N₃O₃·2HCl·2H₂O·0.75CHCl₃: C, 56.68; H, 6.43; N, 4.99. Found: C, 56.55; H, 6.19; N, 5.02.

Example 73:
(+)-1,2,3,6-Tetrahydro-1-{N-[3-(4,4-diphenylpiperidin-1-yl)-propyl]}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluoro-phenyl)-4-methoxymethylpyrimidine hydrochloride.

A solution of (+)-6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenoxy)-carbonylpyrimidine (0.160 g) and 3-(4,4-diphenyl-piperidin-1-yl)propylamine (0.150 g) in tetrahydrofuran (10 mL) was stirred at room temperature for 14 hours. The product was purified by preparative thin layer chromatography on silica gel using ethyl acetate as eluent to give 0.22 g of the product as a syrup, which was converted to the hydrochloride salt by treatment with 1N HCl in ether; m.p. 178-181 °C; $[\alpha]_D = +99.6$ (c = 0.24, MeOH). Anal. Calcd. for C₃₅H₃₉ClF₂N₄O₅·0.2CH₂Cl₂: C, 60.93; H, 5.74; N, 8.06. Found: C, 60.73; H, 5.89; N, 7.92.

Example 74:
(±)-1,2,3,6-Tetrahydro-1-{N-[3-(4,4-diphenylpiperidin-1-yl)-propyl]}carboxamido-5-acetyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methoxymethylpyrimidine dihydrochloride.
A mixture of 6-(3,4,5-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-

5-acetyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.150 g) and 3-(4,4-diphenylpiperidin-1-yl)propylamine (0.180 g) in THF (10 mL) was stirred at room temperature for 14 h. The product was purified by preparative thin layer chromatography on silica gel using ethyl acetate as eluent to give 0.23 g of the product as a syrup, which was converted to the hydrochloride salt by treatment with 1N HCl in ether; m.p. 180-182 °C.

10 Anal. Calcd. for $C_{34}H_{36}ClF_3N_4O_3 \cdot 1CH_2Cl_2$: C, 57.90; H, 5.28; N, 7.72. Found: C, 57.54; H, 5.10; N, 7.79.

Example 75:

(\pm)-1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-methylphenyl)-4-(4-methylphenyl)piperidin-1-yl)-propyl]carboxamido-5-acetyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methylpyrimidine hydrochloride.

A mixture of 6-(3,4,5-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-acetyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.02 g) and 3-[4-(2-methylphenyl)-4-(4-methylphenyl)-piperidin-1-yl]-propylamine (0.02 g) in THF (1 mL) was stirred at room temperature for 14 h. The product was purified by preparative thinlayer chromatography on silica gel using ethyl acetate as eluent to give 0.03 g of the product as a syrup, which was converted to the hydrochloride salt by treatment with 1N HCl in ether; m.p. 180-184 °C.

20 Anal. Calcd. for $C_{36}H_{40}ClF_3N_4O_3 \cdot 0.4CH_2Cl_2$: C, 62.18; H, 5.85; N, 7.97. Found: C, 62.42; H, 6.00; N, 7.88.

Example 76:

(+)-6-(3,4-Difluorophenyl)-1-[(N-[4-cyano-4-phenyl-piperidin-1-yl]-2,2-difluoropropyl)carboxamido]-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine.

a) 3-[4-Cyano-4-phenyl-piperidin-1-yl] (2-

hydroxypropyl)-phthalimide.

A mixture of 4-cyano-4-phenylpiperidine (10 g, 44.9 mmol) and 2,3-epoxypropylphthalimide (10.94 g, 53.9 mmol) in DMF (100 mL) was stirred and heated at 70 °C for 72 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (1000/28/14) as the eluent, to obtain the desired product as a viscous oil (16.45 g, 86%).

b) 3-[4-Cyano-4-phenyl-piperidin-1-yl](2-oxopropyl)phthalimide.

To a stirred solution of DMSO (3.6 mL, 51.07 mmol) in dichloromethane (100 mL) at -78 °C, oxalyl chloride (2.18 mL, 24.5 mmol) in dichloromethane (15 mL) was added and the mixture was stirred for 3 min. To this, a solution of 3-[4-cyano-4-phenyl-piperidin-1-yl](2-hydroxypropyl)phthalimide (8.70 g, 20.42 mmol) in dichloromethane (25 mL) was added and the stirring was continued for 15 min. It was warmed to room temperature and added 5 mL of water.

The pH of the mixture was adjusted to 10-11 by adding 1N NaOH and the dichloromethane layer was separated.

The aqueous layer was extracted with more dichloromethane (3 X 100 mL). The combined dichloromethane extracts were dried (magnesium sulfate), solvents evaporated, and the residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as eluent (6.05 g, 70%).

c) 3-[4-Cyano-4-phenyl-piperidin-1-yl](2,2-difluoropropyl)-phthalimide.

To a well stirred solution of 3-[4-cyano-4-phenyl-piperidin-1-yl]- (2-oxopropyl)phthalimide (0.22 g, 0.52 mmol) in anhydrous dichloromethane (25 mL) at -78°C, under argon atmosphere was added diethyaminosulfur trifluoride (DAST) (0.251 mg, 1.56 mmol) and the mixture was allowed to warm to room

temperature. After 36 h, the reaction mixture was cooled to 0-5 °C and to this saturated sodium bicarbonate solution (20 mL) was added cautiously.

5 The dichloromethane layer was separated, dried (sodium sulfate), and the solvent was evaporated.

The product was purified by flash column chromatography on silica gel using 30% ethyl acetate in hexanes as eluent (80 mg, 38%). ¹H-NMR was in agreement with the product.

10 d) 3-[4-Cyano-4-phenylpiperidin-1-yl](2,2-difluoro)propylamine.

A mixture of 3-[4-cyano-4-phenyl-piperidin-1-yl](2,2-difluoro-propyl)phthalimide (120 mg, 0.29 mmol) and hydrazine (0.5 mL g) in methanol (15 mL) was stirred 15 and refluxed for 4.5 h. It was cooled, filtered, and the solid was washed with methanol (30 mL).

Evaporation of solvent from the filtrate gave the product as a viscous oil (60 mg, 73%) which was used in the next step without any further purification.

20 e) (+)-6-(3,4-Difluorophenyl-1-[(N-[4-cyano-4-phenyl-piperidin-1-yl]-2,2-difluoropropyl)-carboxamido]-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine.

A solution of (+)-5-methoxycarbonyl-4-methoxymethyl-25 1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)-carbonyl]pyrimidine (38 mg, 0.077 mmol) and 3-[4-cyano-4-phenyl-piperidin-1-yl](2,2-difluoropropyl)propylamine (30 mg, 0.107 mmol) in dichloromethane (3 mL) was stirred at room

30 temperature for 12 hours. The mixture was purified by preparative tlc on silica gel (60% ethyl acetate in hexanes) to give 38 mg (81%) as a white powder.

The HCl salt was prepared by treatment of a solution of the free base in ether with 1N HCl in ether. The 35 white powder was dried and recrystallized from anhydrous 2-propanol. M.P. 184-186 °C; [α]_D = +96.36 (c = 0.55, dichloromethane). Anal. Calcd. for

$C_{30}H_{32}N_5O_5F_4Cl:C$, 55.12; H, 4.87; N, 9.95. Found: C, 55.09; H, 4.93; N, 9.71.

Example 77:

(+)-1,2,3,6-Tetrahydro-1-{N-[4-(4-methoxycarbonyl-4-phenyl-piperidin-1-yl)-piperidinyl]carbonyl-5-methoxycarbonyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methoxymethylpyrimidine hydrochloride.

10 a) 1-Benzyl-4-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)-piperidine.

A mixture of 4-methoxycarbonyl-4-phenylpiperidine (6.50 g, 0.0296 mol), N-benzyl-4-piperidone (5.62 g), and p-toluenesulfonic acid (100 mg) in benzene (100 mL) was heated at 110 °C for 14 h with a Dean-Stark trap to remove the water that formed. Solvent was evaporated and the residue was redissolved in methanol (20 mL). To this, sodium cyanoborohydride (1.86 g) was added in portions and the mixture was stirred at room temperature for 6 h. Solvent was evaporated, the residue was mixed with 1N NaOH (10 mL) and the resultant mixture was extracted with ether (4 X 20 mL). The combined extracts were washed with brine (20 mL), dried (sodium sulfate), and the solvent evaporated. The residue was purified by column chromatography on silica gel using dichloromethane/methanol/2M ammonia in methanol (50/20/10) as eluent. The product was obtained as a viscous oil (8.5 g), which on trituration with hexane became a white powder.

30 b) 4-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)-piperidine.

A mixture of 1-benzyl-4-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)piperidine (3.92 g) and 10% Pd-C (0.4 g) in ethanol (200 mL) was hydrogenated at 80 psi for 12h. The catalyst was removed by filtration and the solvent was evaporated from the filtrate to

leave the product (2.9 g, 96%) as a white powder.

c) (+)-1,2,3,6-Tetrahydro-1-[N-[4-(4-methoxycarbonyl-4-phenyl-

5 piperidin-1-yl)-piperidinyl]carbonyl-5-methoxycarbonyl-2-oxo-6-

(3,4,5-trifluorophenyl)-4-methoxymethylpyrimidine hydrochloride.

A solution of (+)-6-(3,4,5-trifluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methoxymethyl-1-

10 (4-nitrophenoxy)-carbonylpyrimidine (50 mg, prepared similarly to (+)-6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methoxy-methyl-1-(4-nitrophenoxy)carbonylpyrimidine) and 4-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)piperidine (50

15 mg) in THF (2 mL) was stirred at room temperature for 14 hours. The product was purified by preparative thin layer chromatography on silica gel using ethyl acetate as eluent to give 70 mg of the product as a syrup, which was converted to the hydrochloride salt

20 by treatment with 1N HCl in ether; m.p. 178-181 °C;

[α]_D = +135 (c = 0.65, MeOH). Anal. Calcd. for

C₃₅H₃₈ClF₃N₄O₇.0.4CH₂Cl₂: C, 55.02; H, 5.36; N, 7.68.

Found: C, 55.22; H, 5.48; N, 7.56.

Example 78:

25 (+)-1,2,3,6-Tetrahydro-1-[N-[2-(4-phenyl-4-methoxycarbonyl)-piperidin-1-yl)ethyl]acetamido-5-methoxycarbonyl-2-oxo-6-

(3,4-difluorophenyl)-4-methylpyrimidine

hydrochloride.

30 a)

(+)-1,2,3,6-Tetrahydro-1-[bezylloxycarbonylmethyl]-5-methoxy-

carbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine.

35 A mixture of (+)-1,6-dihydro-5-methoxycarbonyl-2-methoxy-

6-(3,4-difluorophenyl)-4-methylpyrimidine (0.296 g),

benzyl bromoacetate (0.229 g), potassium carbonate (0.600 g), and potassium iodide (30 mg) in acetone (20 mL) was heated under reflux for 14 h. It was filtered, washed with acetone (15 mL). To the
5 combined filtrates 6N HCl (0.5 mL) was added and stirred for 4 h. Solvent was evaporated and the product was purified by preparative thin layer chromatography on silica gel using hexane/ethyl acetate (1:1) to give the product as a foam (0.20 g)
10 which was used in the next step without further characterization.

b) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine-1-acetic acid.

15 To a suspension of 10% Pd-C (20 mg) in MeOH (10 mL) and H₂O (2 mL) was added a solution of (+)-1,2,3,6-tetrahydro-1-(benzyloxy-carbonylmethyl)-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine (200 mg) in methanol (1 mL) and
20 the mixture was hydrogenated at 80 psi for 4 h. The black suspension was filtered through a pad of Celite and washed thoroughly with MeOH (100 mL). Solvent was evaporated from the combined filtrate to yield the product (+)-1,2,3,6-tetrahydro-1-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine-1-acetic acid
25 as a white solid (0.15 g). It was used in the next step without further purification.

c) (+)-1,2,3,6-Tetrahydro-1-{N-[2-(4-phenyl-4-methoxycarbonyl)-piperidin-1-yl]ethyl}acetamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine hydrochloride.

30 A mixture of (+)-1,2,3,6-tetrahydro-1-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine-1-acetic acid (20 mg), 2-(4-phenyl-4-

methoxycarbonyl)piperidin-1-yl)ethylamine (20 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (20 mg), and 4-(N,N-dimethylamino)pyridine (20 mg) in anhydrous dichloromethane (4 mL) was stirred at room temperature for 12 h. The reaction mixture was purified by preparative thin layer chromatography on silica gel using ethyl acetate as the eluent. The product was dissolved in ether (0.5 mL), cooled to 0-5 °C and treated with 1N HCl in ether (10 mL) and the solvents evaporated to leave the product as a white powder (25 mg); mp 247-250°C; $[\alpha]_D = +108.2$ ($c = 0.50$, MeOH). Anal. Calcd. for $C_{30}H_{35}N_4O_6F_2Cl$: C, 58.02; H, 5.68; N, 9.02. Found: C, 58.21; H, 5.70; N, 8.92.

15 Example 79:

1,6-Dihydro-1-{N-[2-(4-phenyl-4-methoxycarbonyl)piperidin-1-yl)-ethyl]}acetamido-5-methoxycarbonyl-6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine dihydrochloride.
20 a) 6-(3,4,5-trifluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine.

To a solution of acetamidine hydrochloride (1.41 g, 14.9 mmol.) In DMF (10 mL) was added a solution of potassium tert-butoxide (12 mL, 1.0 M in THF) at 0°C. After stirred for 10 minutes, a solution of methyl {2-(3,4,5-trifluorophenyl)methylene}-3-oxobutanoate (2.10 g, 10.0 mmol) in DMF (10 mL) was added and the mixture was stirred for 2 hours while warmed up to room temperature. p-Toluenesulfonic acid monohydrate (4.50 g, 23.6 mmol) was added to the solution and the reaction mixture was heated at 110-120 °C for 2 hours. The mixture was cooled to room temperature and poured into ice (100 g) and aqueous NaOH solution (3 N, 200 mL), and extracted with ether (3x100 mL). The organic layers were combined, dried (K_2CO_3) and evaporated. The residue was purified by flash chromatography over silica gel (eluent: 10-15% MeOH in methylene

chloride) to afford the product in 47% yield (1.4 g) as an oil.

b) 1,6-Dihydro-1-{bezyloxycarbonylmethyl)-5-methoxycarbonyl-

5 6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine. A mixture of 1,6-dihydro-5-methoxycarbonyl-6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine (0.298 g), benzyl bromoacetate (0.229 g), potassium carbonate (0.600 g), and 10 potassium iodide (30 mg) in acetone (20 mL) was heated under reflux for 14 h. It was filtered, washed with acetone (15 mL). Solvent was evaporated and the product was purified by preparative thin layer chromatography on silica gel using hexane/ethyl 15 acetate (1:1) to give the product as a foam (0.34 g). NMR confirmed it to be the desired product which was used in the next step without any further characterization.

c) 1,6-Dihydro-5-methoxycarbonyl-6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine-1-acetic acid. To a suspension 20 of 10% Pd-C (30 mg) in MeOH (10 mL) and H₂O (2 mL) was added a solution of 1,6-dihydro-1-{bezyloxycarbonylmethyl)-5-methoxycarbonyl- 25 6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine (300 mg) in methanol (1 mL) and the mixture was hydrogenated at 80 psi for 4 h. The black suspension was filtered through a pad of Celite and washed 30 thoroughly with MeOH (100 mL). Solvent was evaporated from the combined filtrate to leave the product 1,6-dihydro-5-methoxycarbonyl-6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine-1-acetic acid as a white solid (0.225 g). 35 It was used in the next step without further purification.

d) 1,6-Dihydro-1-{N-[2-(4-phenyl-4-

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methoxycarbonyl)piperidin-1-yl)ethyl] }acetamido-5-
methoxycarbonyl-6-(3,4,5-trifluoro-phenyl)-
2,4-dimethylpyrimidine dihydrochloride.

A mixture of 1,6-dihydro-5-
5 methoxycarbonyl-6-(3,4,5-trifluoro-phenyl)-
2,4-dimethylpyrimidine-1-acetic acid (20 mg), 2-(4-
phenyl-4-methoxycarbonyl)piperidin-1-yl)ethylamine
(20 mg), 1-(3-dimethyl-aminopropyl)-3-
ethylcarbodiimide hydrochloride (20 mg), and 4-(N,N-
10 dimethylamino)pyridine (20 mg) in anhydrous
dichloromethane (4 mL) was stirred at room
temperature for 12 h. The reaction mixture was
purified by preparative thin layer chromatography on
silica gel using ethyl acetate as the eluent. The
15 product was dissolved in ether (0.5 mL), cooled to 0-
5 °C and treated with 1N HCl in ether (10 mL) and the
solvents evaporated to leave the product as a white
powder (25 mg); m.p. 187-190 °C; Anal. Calcd. for
 $C_{11}H_{13}N_4O_5F_3Cl_2$: C, 55.28; H, 5.54; N, 8.32. Found: C,
20 55.36; H, 5.80; N, 8.41.

Example 80:

(+)1,2,3,6-Tetrahydro-1-{N-[4-(2-nitrophenyl)piperazin-1-yl]-propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

a) 1-(2-nitrophenyl)-piperazine.
A heterogenous reaction mixture containing 2-bromo-1-nitrobenzene (2.02 g, 10.0 mmol) and piperazine (4.3 g, 50.0 mmol) was heated at 100°C for 10 h. The orange-red solid was extracted with ethyl acetate and washed thoroughly with 3 N NaOH solution followed by brine. The organic layer was separated and dried over Na_2SO_4 , filtered and the solvent was removed in vacuo. The resulting red oil was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield 1-(2-nitrophenyl)-piperazine as an orange-red oil (1.90 g, 92%). It was converted to its hydrochloride salt.

Anal. calcd. for $C_{10}H_{14}N_3O_2Cl$.0.10 CHCl₃: C, 47.46; H, 5.56; N, 16.44. Found: C, 47.63; H, 5.69; N, 16.42.

b) (+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-nitrophenyl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

To a solution of (+)-1-(3-bromo-propylcarbamoyl)-6-(3,4-difluoro-phenyl)-4-methyl-2-oxo-1,6-dihydro-pyrimidine-5-carboxylic acid methyl ester (0.22 g, 0.5 mmol) and 1-(2-nitro-phenyl)-piperazine (0.15 g, 0.75 mmol) in 20 mL of anhydrous acetone was added powdered K₂CO₃ (0.34 g, 3.5 mmol) and KI (0.07 g, 0.5 mmol) and the resulting suspension was heated to reflux for 10 h. The suspension was cooled, filtered and the solvent was evaporated and the residue was purified by column chromatography on silica gel with EtOAc/MeOH (5:1) as the eluting system. (+)-1,2,3,6-tetrahydro-1-{N-[4-(2-nitrophenyl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine was obtained as a yellow oil (0.08 g, 29% yield). The product was analyzed as its hydrochloride salt. M.P. 133-136°C; [α]_D = +56.7 (c = 0.11, MeOH). Anal. calcd. for C₂₇H₃₁N₅F₂O₆Cl.0.20 CH₂Cl₂: C, 51.62; H, 4.97; N, 13.28. Found: C, 51.35; H, 5.18; N, 11.99.

25 Example 81:

(+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-amino-phenyl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

To a cooled suspension of 10% palladium on carbon (40 mg) in methanol (25 mL) was added a solution of (+)-1,2,3,6-tetrahydro-1-{N-[4-(2-nitrophenyl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine (50 mg, 0.09 mmol) in methanol (5 mL) and the resulting suspension was hydrogenated at 100 psi at room temperature for 3 h. The suspension was filtered through a pad of celite and washed with 50 mL of methanol. The solvent was

removed in vacuo from the combined filtrate to get 0.03 g (60%) of (+)-1,2,3,6-tetrahydro-1-{N-[4-(2-amino-phenyl)-piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluoro-phenyl)-2-oxo-pyrimidine as a yellow oil. No purification was performed on this material and it was characterized as its dihydrochloride salt. Mass spectrum (low res.) 543 (M+1, 100%); $[\alpha]_D = +75.1$ ($c = 0.41$, MeOH); Anal calcd. for $C_{21}H_{34}N_6F_2O_4Cl_2$.0.03 CHCl₃: C, 52.48; H, 5.54; N, 13.59. Found: C, 52.35; H, 5.83; N, 12.50.

Example 82:

1,2,3,6-Tetrahydro-1-{N-[4-(6-(nitro)pyrid-2-yl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

a) 1-[6-(nitro)pyrid-2-yl]piperazine.
To a solution of 2-chloro-3-nitropyridine (1.58 g, 10.0 mmol) in 1,4-dioxane (50 mL) was added piperazine (4.3 g, 50.0 mmol) and powdered K₂CO₃ (50.0 mmol, 6.9 g) and the resulting suspension was heated at reflux for 10 h. After the suspension was cooled, it was extracted with ethyl acetate (2 X 50 mL) and washed successively with 3 N NaOH (20 mL) and water (20 mL). The organic layer was dried over Na₂SO₄, filtered and the solvent was removed in vacuo. The resulting residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield 1-[6-(nitro)pyrid-2-yl]piperazine as a yellow solid. It was characterized as a hydrochloride salt.

Anal calcd. for $C_9H_{12}N_4O_2Cl$.0.25 CHCl₃: C, 40.47; H, 4.86; N, 20.41. Found: C, 40.72; H, 4.97; N, 20.50.

b) 1,2,3,6-Tetrahydro-1-{N-[4-(6-(nitro)pyrid-2-yl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

To a solution of 1-(3-bromo-propylcarbamoyl)-6-(3,4-difluoro-phenyl)-4-methyl-2-oxo-1,6-dihydro-pyrimidine-5-carboxylic acid methyl ester (0.04 g,

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0.1 mmol) and 1-[6-(nitro)pyrid-2-yl]-piperazine (0.03 g, 0.15 mmol) in 10 mL of anhydrous acetone was added powdered K₂CO₃ (0.06 g, 0.6 mmol) and KI (0.01 g, 0.10 mmol) and the resulting suspension was heated 5 to reflux for 10 h. The suspension was cooled, filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel with EtOAc/MeOH (5:1) as the eluting system. 1,2,3,6-tetrahydro-1-{N-[4-(6-(nitro)pyrid-2-yl)-piperazin-1-yl]propyl}-carboxamido-4-methyl-6- (3,4-difluoro-phenyl)-2-oxo-pyrimidine was obtained 10 as a yellow oil (0.04 g, 70% yield). The product was analyzed as its hydrochloride salt. M.P. 142-145°C; Anal calcd. for C₂₆H₃₀N₂F₂O₆Cl_{0.30} CH₂Cl₂: C, 48.91; H, 4.74; N, 15.18. Found: C, 48.94; H, 4.94; N, 13.29.

15 Example 83:
(+)-1,2,3,6-Tetrahydro-1-{N-[2-(S)-methyl]-4-(2-nitrophenyl)-piperazin-1-yl}propyl}-carboxamido-4-methyl-6-(3,4-difluoro-phenyl)-2-oxo-pyrimidine.
20 a) (S)-(+)-3-methyl-1-(2-nitrophenyl)piperazine.
To a solution of 2-bromo-1-nitrobenzene (0.6 g, 3.0 mmol) in 1,4-dioxane (15 mL) was added (S)-(+)-2-methylpiperazine (0.5 g, 0.5 mmol) and powdered K₂CO₃ (15.0 mmol, 1.5 g) and the resulting suspension was 25 heated at reflux for 10 h. After the suspension was cooled, it was filtered through a sintered glass funnel and the solvent was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield (S)-(+)-3-methyl-1-(2-nitrophenyl)-piperazine as an orange oil 30 (0.53 g, 80%).
b) (+)-1,2,3,6-Tetrahydro-1-{N-[2-(S)-methyl]-4-(2-nitrophenyl)-piperazin-1-yl}propyl}-carboxamido-4-methyl-6-(3,4-difluoro)-phenyl-2-oxo-pyrimidine.
35 To a solution of (+)-1-(3-bromopropylcarbamoyl)-6-(3,4-difluorophenyl)-4-methyl-2-oxo-1,6-dihydro-

pyrimidine-5-carboxylic acid methyl ester (0.2 g, 0.5 mmol) and (*S*)-(+)-3-methyl-1-(2-nitrophenyl)piperazine (0.17 g, 0.75 mmol) in 20 mL of anhydrous acetone was added powdered K₂CO₃ (0.34 g, 3.5 mmol) and KI (0.07 g, 0.5 mmol) and the resulting suspension was heated to reflux for 10 h. TLC indicated a new spot for the product (R_f = 0.3, 3:0.5 EtOAc/MeOH) and mostly the starting material. The suspension was cooled, filtered and the solvent was evaporated and the residue was purified by column chromatography on silica gel with EtOAc/MeOH (5:1) as the eluting system. (+)-1,2,3,6-Tetrahydro-1-{N-[2-(*S*-methyl)-4-(2-nitrophenyl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine was obtained as yellow oil (0.03 g, 10% yield). The product was analyzed as its hydrochloride salt. M.P. 150-153°C; [α]_D = 58.3 (c = 0.3, MeOH); Anal calcd. for C₂₈H₃₃N₆F₂O₆Cl_{0.20} CH₂Cl₂: C, 52.92; H, 5.26; N, 13.13. Found: C, 52.84; H, 5.68; N, 12.94.

Example 84:

A) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[2-(*R*-methyl)-4-(2-nitrophenyl)piperazin-1-yl]propyl}-6-(3,4-difluorophenyl)pyrimidine.

a) (*R*)-(+) -3-methyl-1-(2-nitrophenyl)piperazine.

To a solution of 2-bromo-nitrobenzene (0.4 g, 2.0 mmol) in 1,4-dioxane (10 mL) was added (*R*)-(+) -2-methylpiperazine (0.25 g, 0.25 mmol) and powdered K₂CO₃ (7.5 mmol, 0.8 g) and the resulting suspension was heated at reflux for 10 h. After the suspension was cooled, it was filtered through a sintered glass funnel and the solvent was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield (*R*)-(+) -3-methyl-1-(2-nitrophenyl)-piperazine as an orange-red oil (0.26 g, 78%).

b) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[2-(R)-methyl]-4-(2-nitrophenyl)piperazin-1-yl}propyl}-6-(3,4-difluorophenyl)pyrimidine.

To a solution of (+)-1-(3-bromo-propylcarbamoyl)-6-(3,4-difluorophenyl)-4-methyl-2-oxo-1,6-dihydro-pyrimidine-5-carboxylic acid methyl ester (0.11 g, 0.25 mmol) and (R)-(+)-3-methyl-1-(2-nitrophenyl)-piperazine (0.11 g, 0.50 mmol) in 20 mL of anhydrous acetone was added powdered K₂CO₃, (0.34 g, 3.5 mmol) and KI (0.07 g, 0.5 mmol) and the resulting suspension was heated to reflux for 10 h. TLC indicated a new spot for the product (Rf = 0.3, 3:0.5 EtOAc/MeOH) and mostly the starting material. The suspension was cooled, filtered and the solvent was evaporated and the residue was purified by column chromatography on silica gel with EtOAc/MeOH (5:1) as the eluting system. (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[2-(R)-methyl]-4-(2-nitrophenyl)piperazin-1-yl}propyl}-6-(3,4-difluorophenyl)-pyrimidine was obtained as yellow oil (0.02 g, 14% yield). The product was analyzed as its hydrochloride salt. M.P. 135-138°C; [α]_D = + 63.5 (c = 0.2, MeOH); Anal calcd. for C₂₈H₃₁N₆F₂O₆Cl 1.0 CHCl₃: C, 46.92; H, 4.62; N, 11.32. Found: C, 46.94; H, 4.97; N, 11.47.

Example 85:

(+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]propyl}-6-(3,4-difluorophenyl) pyrimidine.

a) 4-(2-Methoxy-5-methyl)phenyl-4-phenylpiperidine hydrochloride.

To a 100 mL round bottom flask equipped with a rubber septum and a stirring bar was added 4-hydroxy-4-phenyl-piperidine (1.25 g, 7.0 mmol) followed by 10 mL of 4-methylanisole. The resulting solution was stirred at room temperature under argon atmosphere

and then AlCl₃ (2.82 g, 21.0 mmol) was added in one portion. An exotherm was observed. The reaction mixture was stirred for 8 h and then poured carefully over 150 ml of ice-water. The white solid that precipitated out was filtered and washed thoroughly with water followed by diethyl ether to obtain 4-(2-methoxy-5-methyl)-phenyl-4-phenyl-piperidine hydrochloride (1.59 g, 50%) as a white solid. Mass spectrum: 282 (M+1, 100%). Anal calcd. for C₁₉H₂₄NOCl_{0.15} CH₂Cl₂: C, 69.57; H, 7.41; N, 4.24. Found: C, 69.62; H, 7.31; N, 4.36.

b) 3-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]-propylamine.
To a solution of 4-(2-methoxy-5-methyl)-phenyl-4-phenyl-piperidine (0.6 g, 2.1 mmol) in 30 mL dioxane was added 3-bromo-N-tert-butoxycarbonyl-propylamine (0.6 g, 2.5 mmol) and K₂CO₃ (0.6 g, 6.0 mmol) and the resulting suspension was heated to reflux for 10 h. The suspension was allowed to cool, filtered and the solvent was evaporated to obtain yellow residue which was purified by column chromatography (R_f = 0.4, 3:1 EtOAc/MeOH) to obtain 3-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]-N-tert-butoxycarbonyl-propylamine as a yellow oil (0.35 g). It was dissolved in 15 mL of CH₂Cl₂ and 3.0 mL of trifluoroacetic acid was added with stirring at room temperature under argon atmosphere for 1 h. The solvent was evaporated in vacuo and the residue was basified to pH 10 by adding minimum amount of 1 N KOH solution. The product was extracted with CH₂Cl₂ (3 X 25 mL), dried over MgSO₄, filtered and the solvent was removed in vacuo to obtain 3-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]propylamine as a yellow oil (0.25 g, 35% for two steps). It was used in the next step without further purification.
c) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-methoxy-5-

methyl)phenyl-4-phenyl-piperidin-1-yl]propyl}-6-(3,4-difluorophenyl) pyrimidine.

To a solution of 3-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]propylamine (0.12 g, 0.36 mmol) in 5.0 mL THF was added (+)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-(4-nitrophenyloxy)carbonyl-6-(3,4-difluorophenyl)pyrimidine (0.12 g, 0.33 mmol) at room temperature and the resulting yellow solution was stirred for 6 h. The solvent was removed in vacuo and the resulting residue was subjected to column chromatography over silica gel (1:1 hexane/EtOAc to EtOAc to 9:1 EtOAc/MeOH) to obtain (+)-1,2,3,6-tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]propyl}-6-(3,4-difluorophenyl)pyrimidine (0.12 g, 65%) as a yellow oil. It was converted into its HCl salt (pale yellow powder). M.P. 102-105°C. $[\alpha]$ _D = + 49.4 (c = 0.65, MeOH) Anal calcd. for C₃₂H₃₆N₃O₄F₂Cl·1.5 CH₂Cl₂: C, 55.31; H, 5.40; N, 5.78. Found: C, 55.55; H, 5.06; N, 6.08.

Example 86:

(+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(4-methyl)-phenyl-4-(2-methyl)phenyl piperidin-1-yl]-propyl}-6-(3,4-difluorophenyl) pyrimidine.

a) 4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidine hydrochloride.

To a 100 mL round bottom flask equipped with a rubber septum and a stirring bar was added 4-hydroxy-4-(4-methyl)phenyl-piperidine (1.25 g, 6.54 mmol) followed by 20 mL of anhydrous toluene. The resulting solution was stirred at room temperature under argon atmosphere and then AlCl₃ (1.4 g, 10.2 mmol) was added in one portion. An exotherm was observed. The reaction mixture was stirred for 10 h and then poured carefully over 100 ml of ice-water. The white solid

that precipitated out was filtered and washed thoroughly with water followed by diethyl ether to obtain 4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidine hydrochloride (1.95 g, 99%) as a white solid. Mass spectrum: 266 (M+1, 100%).
Anal calcd. for C₁₉H₂₄NCl.0.15 CH₂Cl₂: C, 73.11; H, 7.79; N, 4.45. Found: C, 73.33; H, 7.82; N, 3.92.

b) 3-[4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidin-1-yl]-propylamine.

To a solution of 4-(4-methyl)-phenyl-4-(2-methyl)phenyl piperidine hydrochloride (2.6 g, 9.8 mmol) in 100 mL dioxane was added 3-bromo-N-tert-butoxycarbonyl-propylamine (2.57 g, 10.8 mmol) and K₂CO₃ (4.06 g, 29.4 mmol) and the resulting suspension was heated to reflux for 10 h. The suspension was allowed to cool, filtered and the solvent was evaporated to obtain a yellow residue which was purified by column chromatography over silica gel (Rf = 0.4, 3:1 EtOAc/MeOH) to give 3-[4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidin-1-yl]-N-tert-butoxycarbonyl-propylamine as a yellow oil (2.30 g). It was dissolved in 60 mL of CH₂Cl₂, and 10.0 mL of trifluoroacetic acid was added with stirring at room temperature under argon atmosphere for 1 h. The solvent was evaporated in vacuo and the residue was basified to pH 10 by adding minimum amount of 1 N KOH solution. The product was extracted with CH₂Cl₂ (3 X 25 mL), dried over MgSO₄, filtered and the solvent was removed in vacuo to obtain 3-[4-(4-methyl)-phenyl-4-(2-methyl)phenyl piperidin-1-yl]propylamine as a yellow oil (1.39 g, 44% for two steps). It was used in the next step without further purification.

c) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(4-methyl)-phenyl-4-(2-methyl)phenylpiperidin-1-yl]-propyl}-6-(3,4-difluorophenyl)pyrimidine.

To a solution of 3-[4-(4-methyl)phenyl-4-(2-

methyl)phenyl-piperidin-1-yl]propylamine (0.10 g, 0.31 mmol) in 10.0 mL THF was added (+)-1,6-Dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-(4-nitrophenyloxy)carbonyl-6-(3,4-difluorophenyl)pyrimidine (0.10 g, 0.28 mmol) at room temperature and the resulting yellow solution was stirred for 8 h. The solvent was removed in vacuo and the resulting residue was subjected to column chromatography over silica gel (1:1 hexane/EtOAc to EtOAc to 9:1 EtOAc/MeOH) to obtain (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[3-[4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidin-1-yl]propyl]-6-(3,4-difluorophenyl)pyrimidine (0.11 g, 70%) as a yellow oil. It was converted into its HCl salt (pale yellow powder). M.P. 103-107°C. $[\alpha]_D = + 104.8$ ($c = 0.31$, MeOH) Anal calcd. for $C_{38}H_{46}N_4O_5F_2Cl$: C, 60.44; H, 6.32; N, 6.71. Found: C, 60.44; H, 6.21; N, 7.19.

20 Example 87:

(+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[3-(4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidin-1-yl)propyl]-6-(3,4-difluorophenyl)pyrimidine.

To a solution of 3-[4-(4-methyl)phenyl-4-(2-methyl)phenyl-piperidin-1-yl]propylamine (0.25 g, 0.78 mmol) in 10.0 mL THF was added (+)-1,6-dihydro-5-methoxycarbonyl-4-methyl-2-oxo-1-(4-nitrophenyloxy)carbonyl-6-(3,4-difluorophenyl)pyrimidine (0.22 g, 0.67 mmol) at room temperature and the resulting yellow solution was stirred for 8 h. The solvent was removed in vacuo and the resulting residue was subjected to column chromatography over silica gel (1:1 hexane/EtOAc to EtOAc to 9:1 EtOAc/MeOH) to obtain (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[3-[4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidin-1-

yl]-propyl}-6-(3,4-difluorophenyl)pyrimidine (0.19 g, 64%) as a yellow oil. It was converted into its HCl salt (pale yellow powder). M.P. 143-147°C. $[\alpha]_D = + 79.8$ ($c = 0.25$, MeOH). Anal. calcd. for C₁₇H₂₄N₄O₄F₂Cl. 0.50 CH₂Cl₂: C, 62.19; H, 6.26; N, 7.73. Found: C, 62.15; H, 5.92; N, 7.21.

5 Example 88:

10 1,2,3,6-Tetrahydro-1-{[4-benzamido-piperidin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

15 a) 4-Amino-1-benzylpiperidine.

To a solution of hydroxylamine hydrochloride (3.67 g, 52.8 mmol) in water (10 mL) and ethyl alcohol (80 mL) was added 1-benzyl piperidone (10.0 g, 52.8 mmol) at room temperature. The reaction mixture was heated to reflux for 4 h and then stirred at room temperature overnight. The resulting white solid was filtered, washed with ether and dried (8.4 g, 80%). It was added in small portions to a suspension of lithium aluminum hydride (2.3 g, 60.0 mmol) in diethyl ether (150 mL) at room temperature and the suspension was heated to reflux for 8 h. The reaction mixture was cooled to 0°C and quenched with successive addition of water (3 mL), 3 N NaOH (3 mL) and water (9 mL). The white suspension was filtered and the filtrate was dried over MgSO₄. The solvent was removed in vacuo after filtration. 4-Amino-1-benzyl-piperidine was obtained as a colorless oil (6.0 g). It was used in the next step without purification.

20 b) 1-Benzyl-4-benzamidopiperidine.

To a biphasic solution of 4-amino-1-benzylpiperidine (6.0 g, 31.6 mmol), K₂CO₃ (8.71 g, 63.1 mmol) in CH₂Cl₂ (200 mL) and water (100 mL) was added benzoyl chloride (4.86 g, 34.7 mmol) in 20 mL of CH₂Cl₂ at 0°C with stirring. After stirring for 4 h at room temperature, the layers were separated. The organic layer was washed with water, dried over MgSO₄ and

filtered. The solvent was removed in vacuo to obtain 1-benzyl-4-benzamidopiperidine (8.16 g, 87% yield) as a white solid. It was used in the next step without purification.

5 c) 4-Benzamido-piperidine.

To a suspension of 10% palladium on carbon (0.2 g) in 30 mL of ethyl alcohol was added a solution of 1-benzyl-4-benzamido- piperidine (0.5 g, 1.79 mmol) in ethyl alcohol (10 mL). The resulting suspension was 10 hydrogenated at 100 psi at 50°C for 30 h after which it was filtered through a pad of celite and the solvent was removed in vacuo to obtain 0.34 g (100%) of 4-benzamidopiperidine as a white solid. It was used in the next step without purification.

15 d) 1,2,3,6-Tetrahydro-1-[4-benzamido-piperidin-1-yl]propyl]-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

To a solution of 1-(3-bromopropylcarbamoyl)-6-(3,4-difluoro-phenyl)-4-methyl-2-oxo-1,6-dihydropyrimidine-5-carboxylic acid methyl ester (0.04 g, 0.10 mmol) and 4-benzamidopiperidine (0.03 g, 0.15 mmol) in 15 mL of anhydrous THF was added triethylamine (2 mL) and the resulting solution was heated to reflux for 10 h. The suspension was 20 cooled, filtered and the solvent was evaporated. The residue was purified by column chromatography on silica gel with EtOAc/MeOH (5:1) as the eluting system. 1,2,3,6-tetrahydro-1-[4-benzamidopiperidin-1-yl]propyl]carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine was obtained as a yellow oil (0.02 g, 37% yield). The product was analyzed as its hydrochloride salt. M.P. 121-125°C. Anal calcd. for C₂₉H₃₄N₅F₂O₅Cl: 0.53 CHCl₃: C, 53.03; H, 5.20; N, 10.37. Found: C, 52.90; H, 5.61; N, 9.97.

25 Example 89:

4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-[3-(4-phenyl-4-(thiophen-2-yl)piperidin-1-yl)-

propylcarbamoyl}-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.

a) 4-Phenyl-4-(thiophen-2-yl)piperidine.

To a solution of 4-hydroxy-4-phenylpiperidine (1.0 g, 5.6 mmol) and thiophene (0.88 ml, 11 mmol) in 20 ml of CH₂Cl₂, was added AlCl₃ (0.75 g, 5.6 mmol) at -78 °C and the resulting reaction mixture was stirred for 1 h. The reaction mixture was basified with sat'd aqueous NaHCO₃, and extracted with EtOAc. The organic layer was dried over Na₂CO₃, and concentrated in vacuo to provide the product as a colorless oil which was subjected to the following reaction without further purification.

b) 3-(4-Phenyl-4-(thiophen-2-yl)piperidin-1-yl)propylamine.

A solution of 4-phenyl-4-(thiophen-2-yl)piperidine and 3-Boc-aminopropylbromide (1.0 g, 4.4 mmol) with 1 g of K₂CO₃, in 20 ml of dioxane was stirred at reflux for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic solution was dried over Na₂SO₄, and concentrated in vacuo to yield an oil which was subjected to column chromatography over silica gel (EtOAc) to provide 0.43 g (1.1 mmol, 20% for two steps) of 3-(4-phenyl-4-(thiophene-2-yl)piperidin-1-yl)-propylcarbamic acid tert-butyl ester as colorless oil. The ester in 5 ml of CH₂Cl₂, was added with 1 ml of CF₃CO₂H and resulting solution was stirred for 1 h at 25 °C. The reaction mixture was concentrated in vacuo to yield oily mixture, which was dissolved in EtOAc and washed with aqueous NaHCO₃. Concentration of the reaction mixture provided the desired product as an oil (0.29 g, 0.96 mmol, 88%) which was used in the next step without further purification.

c) 4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-[3-(4-phenyl-4-(thiophen-2-yl)piperidin-1-yl)propylcarbamoyl]-1,2,3,4-tetrahydropyrimidine-5-

carboxylic acid methyl ester.

To a solution of 6-(3,4-difluorophenyl)-4-methoxymethyl-2-oxo-3,6-dihydro-2H-pyrimidine-1,5-dicarboxylic acid 5-methyl ester 1-(4-nitrophenyl)ester (29 mg, 0.06 mmol) in 2 ml of CH₂Cl₂, was added 3-(4-phenyl-4-thiophen-2-yl-piperidin-1-yl)propylamine (20 mg, 0.07 mmol) and the resulting solution was stirred for 2 h at 25 °C. The reaction mixture was concentrated in vacuo to provide an oil which was subjected to column chromatography over silica gel (5% MeOH/CHCl₃) to yield 25 mg (64%) of the desired product which was converted to a HCl salt and recrystallized from EtOAc-Et₂O to afford 22 mg of the product as a white solid: mp 157-159°C; Anal. Calc. For C₃₃H₃₆F₂N₄O₅S requires C, 58.6; H, 5.33; N, 8.29. Found: C, 57.3; H, 5.45; 7.90.

Example 90:

4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-[3-(4-phenyl-4-(furan-2-yl)piperidin-1-yl)propyl]carbamoyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.

a) 4-Phenyl-4-(furan-2-yl)piperidine.

To a solution of 4-hydroxy-4-phenyl-piperidine (0.3 g, 1.7 mmol) and furan (0.50 ml, 6.8 mmol) in 20 ml of CH₂Cl₂ was added AlCl₃ (0.50 g, 3.7 mmol) at 25 °C and the resulting reaction mixture was stirred for 1 h. The reaction mixture was basified with sat'd aqueous NaHCO₃ and extracted with EtOAc. The organic layer was dried over Na₂CO₃ and concentrated in vacuo to provide a colorless oil which was identified as the desired product by NMR analysis and subjected to the following reaction without further purification.

b) 3-(4-Phenyl-4-(furan-2-yl)piperidin-1-yl)propylamine.

A solution of 4-phenyl-4-furan-2-yl-piperidine and 3-Boc-aminopropylbromide (0.30 g, 1.3 mmol) with 0.5 g of K₂CO₃ in 20 ml of dioxane was stirred at reflux for

12 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic solution was dried over Na₂SO₄ and concentrated in vacuo to yield an oil which was subjected to column chromatography over silica gel (EtOAc) to provide 0.21 g (0.54 mmol, 32% for two steps) of 3-(4-phenyl-4-(furan-2-yl)piperidin-1-yl)propylcarbamic acid tert-butyl ester as a colorless oil. The ester in 5 ml of CH₂Cl₂ was added with 1 ml of CF₃CO₂H and resulting solution was stirred for 1 h at 25 °C. The reaction mixture was concentrated in vacuo to yield oily mixture, which was dissolved in EtOAc and washed with aqueous NaHCO₃. Concentration of the reaction mixture provided the desired product as an oil (0.13 g, 0.45 mmol, 84%).

c) 4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-[3-(4-phenyl-4-(furan-2-yl)piperidin-1-yl)propylcarbamoyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.

To a solution of 6-(3,4-difluorophenyl)-4-methoxymethyl-2-oxo-3,6-dihydro-2H-pyrimidine-1,5-dicarboxylic acid 5-methyl ester 1-(4-nitrophenyl)ester (20 mg, 0.04 mmol) in 2 ml of CH₂Cl₂, was added 3-(4-phenyl-4-furan-2-yl-piperidin-1-yl)-propylamine (12 mg, 0.04 mmol) and resulting solution was stirred for 2 h at 25 °C. The reaction mixture was concentrated in vacuo to provide an oil which was subjected to column chromatography over silica gel (5% MeOH/CHCl₃) to yield 22 mg (85%) of the desired product, which was converted to HCl salt and recrystallized from EtOAC-Et₂O to afford 18 mg of the product as a white solid: mp 153-155 °C; Anal. Calc. For C₃₃H₃₆F₂N₄O₆ requires C, 60.1; H, 5.46; N, 8.49. Found: C, 58.9; H, 5.53; 8.45.

35 Example 91:
4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-[3-[4-phenyl-4-(1-methylpyrrol-2-yl)-piperidin-1-yl]-

propylcarbamoyl}-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.

a) 4-Phenyl-4-(1-methylpyrrol-2-yl)piperidine.

To a solution of 4-hydroxy-4-phenylpiperidine (0.5 g, 2.8 mmol) and 1-methylpyrrole (0.50 ml, 5.6 mmol) in 20 ml of CH₂Cl₂, was added AlCl₃ (0.75 g, 5.6 mmol) at 25 °C and the resulting reaction mixture was stirred for 1 h. The reaction mixture was basified with sat'd aqueous NaHCO₃, and extracted with EtOAc. The organic layer was dried over Na₂CO₃, and concentrated in vacuo to provide the desired product as a colorless oil.

b) 3-[4-Phenyl-4-(1-methylpyrrol-2-yl)piperidin-1-yl]-propylamine.

A solution of 4-phenyl-4-(1-methylpyrrol-2-yl)-piperidine and 3-Boc-aminopropylbromide (1.0 g, 4.5 mmol) with 1.5 g of K₂CO₃, in 20 ml of dioxane was stirred at reflux for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. Organic solution was dried over Na₂SO₄, and concentrated in vacuo to yield an oil which was subjected to column chromatography over silica gel (EtOAc) to provide 0.44 g (1.1 mmol, 20% for two steps) of 3-[4-phenyl-4-(1-methylpyrrol-2-yl)-piperidin-1-yl]-propylcarbamic acid tert-butyl ester as a colorless oil. The ester in 10 ml of CH₂Cl₂, was added with 1 ml of CF₃CO₂H and resulting solution was stirred for 1 h at 25 °C. The reaction mixture was concentrated in vacuo to yield an oily mixture, which was dissolved in EtOAc and washed with aqueous NaHCO₃.

Concentration of the reaction mixture provided an oil (0.26 g, 0.87 mmol, 79%) which was identified as the desired product.

c) 4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-[3-[4-phenyl-4-(1-methylpyrrol-2-yl)-piperidin-1-yl]propylcarbamoyl}-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.

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To a solution of 6-(3,4-difluorophenyl)-4-methoxymethyl-2-oxo-3,6-dihydro-2H-pyrimidine-1,5-dicarboxylic acid 5-methyl ester 1-(4-nitrophenyl)ester (24 mg, 0.05 mmol) in 2 ml of CH₂Cl₂, 5 was added 3-[4-phenyl-4-(1-methylpyrrol-2-yl)-piperidin-1-yl]-propylamine (15 mg, 0.05 mmol) and resulting solution was stirred for 2 h at 25 °C. Reaction mixture was concentrated in vacuo to provide 10 an oil which was subjected to column chromatography over silica gel (5% MeOH/CHCl₃) to yield 22 mg (69%) of the desired product, which was converted to HCl salt and recrystallized from EtOAC-Et₂O to afford 16 mg of the product as a white solid: mp 139-142°C.

15 Example 92

As a specific embodiment of an oral composition of a compound of this invention, 100mg of one of the compounds described herein is formulated with sufficient finely divided lactose to provide a total 20 amount of 580 to 590 mg to fill a size O hard gel capsule.

Pharmacological Profiles of the Compounds in Cloned Human Adrenergic Receptors.

5 Binding affinities were measured for selected compounds of the invention at six cloned human alpha-1 and alpha-2 receptor subtypes, as well as at the L-type calcium channel. The protocols for these experiments are given below.

10 Protocol for the Determination of the Potency of α_1 Antagonists

15 The activity of compounds at the different human receptors was determined in vitro using cultured cell lines that selectively express the receptor of interest. These cell lines were prepared by transfecting the cloned cDNA or cloned genomic DNA or constructs containing both genomic DNA and cDNA encoding the human α -adrenergic receptors as follows:

20 **α_{1B} Human Adrenergic Receptor:** The entire coding region of α_{1B} (1719 bp), including 150 base pairs of 5' untranslated sequence (5' UT) and 300 bp of 3' untranslated sequence (3' UT), was cloned into the BamHI and ClaI sites of the polylinker-modified eukaryotic expression vector pCEXV-3, called EXJ.HR. The construct involved the ligation of partial overlapping human lymphocyte genomic and hippocampal cDNA clones: 5' sequence were contained on a 1.2 kb SmaI-XhoI genomic fragment (the vector-derived BamHI site was used for subcloning instead of the internal insert-derived SmaI site) and 3' sequences were contained on an 1.3 kb XhoI-ClaI cDNA fragment (the ClaI site was from the vector polylinker). Stable cell lines were obtained by cotransfection with the plasmid α_{1A} /EXJ (expression vector containing the α_{1A} receptor gene (old nomenclature)) and the plasmid pGCcos3neo (plasmid containing the aminoglycoside transferase

gene) into LM(tk-) cells using calcium phosphate technique. The cells were grown, in a controlled environment (37°C., 5% CO₂), as monolayers in Dulbecco's modified Eagle's Medium (GIBCO, Grand Island, NY) containing 25mM glucose and supplemented with 10% bovine calf serum, 100 units/ml penicillin g, and 100 µg/ml streptomycin sulfate. Stable clones were then selected for resistance to the antibiotic G-418 (1 mg/ml), and membranes were harvested and assayed for their ability to bind [³H]prazosin as described below (see "Radioligand Binding assays").

The cell line expressing the human α_{1D} receptor used herein was designated L-α_{1A} (old nomenclature) and was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure.

The cell line expressing the human α_{1D} receptor, was accorded ATCC Accession No. CRL 11138, and was deposited on September 25, 1992.

α_{1B} Human Adrenergic Receptor: The entire coding region of α_{1B} (1563 bp), including 200 base pairs and 5' untranslated sequence (5' UT) and 600 bp of 3' untranslated sequence (3' UT), was cloned into the EcoRI site of pCEXV-3 eukaryotic expression vector. The construct involved ligating the full-length containing EcoRI brainstem cDNA fragment from λ ZapII into the expression vector. Stable cell lines were selected as described above. The cell line used herein was designated L-α_{1B} and was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the

Purposes of Patent Procedure. The cell line L- α_{1B} was accorded ATCC Accession No. CR 11139, on September 29, 1992.

5 **α_{1A} Human Adrenergic Receptor:** The entire coding region of α_{1A} (1401 bp), including 400 base pairs of 5' untranslated sequence (5' UT) and 200 bp of 3' untranslated sequence (3' UT), was cloned into the KpnI site of the polylinker-modified pCEXV-3-derived
10 eukaryotic expression vector, EXJ.RH. The construct involved ligating three partial overlapping fragments: a 5' 0.6kb HincII genomic clone, a central 1.8 EcoRI hippocampal cDNA clone, and a 3' 0.6Kb PstI genomic clone. The hippocampal cDNA fragment overlaps with the
15 5' and 3' genomic clones so that the HincII and PstI sites at the 5' and 3' ends of the cDNA clone, respectively, were utilized for ligation. This full-length clone was cloned into the KpnI site of the expression vector, using the 5' and 3' KpnI sites of
20 the fragment, derived from vector (i.e., pBluescript) and 3'-untranslated sequences, respectively. Stable cell lines were selected as described above. The stable cell line expressing the human α_{1A} receptor used herein was designated L- α_{1C} (old nomenclature) and was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure.
25 The cell line expressing the human α_{1A} receptor was accorded Accession No. CR 11140, on September 25, 1992.

30
35 **Radioligand Binding Assays:** Transfected cells from culture flasks were scraped into 5ml of 5mM Tris-HCl, 5mM EDTA, pH 7.5, and lysed by sonication. The cell lysates were centrifuged at 1000 rpm for 5 min at 4°C, and the supernatant was centrifuged at 30,000 x g for

20 min at 4°C. The pellet was suspended in 50mM Tris-HCl, 1mM MgCl₂, and 0.1% ascorbic acid at pH 7.5. Binding of the α₁ antagonist [³H]prazosin (0.5 nM, specific activity 76.2 Ci/mmol) to membrane preparations of LM(tk-) cells was done in a final volume of 0.25 ml and incubated at 37°C for 20 min. Nonspecific binding was determined in the presence of 10 μM phentolamine. The reaction was stopped by filtration through GF/B filters using a cell harvester. Inhibition experiments, routinely consisting of 7 concentrations of the tested compounds, were analyzed using a non-linear regression curve-fitting computer program to obtain Ki values.

15 α₂ Human Adrenergic Receptors: To determine the potency of α₁ antagonists at the α₂ receptors, LM(tk-) cell lines stably transfected with the genes encoding the α_{2A}, α_{2B}, and α_{2C} receptors were used. The cell line expressing the α_{2A} receptor is designated L-α_{2A}, and was deposited on November 6, 1992 under ATCC Accession No. CRL 11180. The cell line expressing the α_{2B} receptor is designated L-NGC-α_{2B}, and was deposited on October 25, 1989 under ATCC Accession No. CRL10275. The cell line expressing the α_{2C} receptor is designated L-α_{2C}, and was deposited on November 6, 1992 under ATCC Accession No. CRL-11181. All the cell lines were deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. Cell lysates were prepared as described above (see Radioligand Binding Assays), and suspended in 25mM glycylglycine buffer (pH 7.6 at room temperature). Equilibrium competition binding assay were performed using [³H]rauwolscine (0.5nM), and nonspecific binding was determined by incubation with 10μM phentolamine. The bound

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radioligand was separated by filtration through GF/B filters using a cell harvester.

5 Determination of the Activity of α_1 Antagonists at Calcium Channels

The potency of α_1 antagonists at calcium channels may be determined in competition binding assays of [3H]nitrendipine to membrane fragments of rat cardiac muscle, essentially as described by Glossman and Ferry (Methods in Enzymology 109:513-550, 1985). Briefly, the tissue is minced and homogenized in 50mM Tris-HCl (pH 7.4) containing 0.1mM phenylmethylsulfonyl fluoride. The homogenates are centrifuged at 1000 g for 15 minutes, and the resulting supernatant 10 centrifuged at 45,000 g for 15 minutes. The 45,000 g pellet is suspended in buffer and centrifuged a second time. Aliquots of membrane protein are then incubated 15 for 30 minutes at 37°C in the presence of [3H]nitrendipine (1nM), and nonspecific binding determined in the presence of 10 μ M nifedipine. The 20 bound radioligand is separated by filtration through GF/B filters using a cell harvester.

25 The compounds described above were assayed using cloned human alpha adrenergic receptors. The preferred compounds were found to be selective α_{1c} antagonists. The binding affinities of compounds 13-17 are illustrated in the following table.

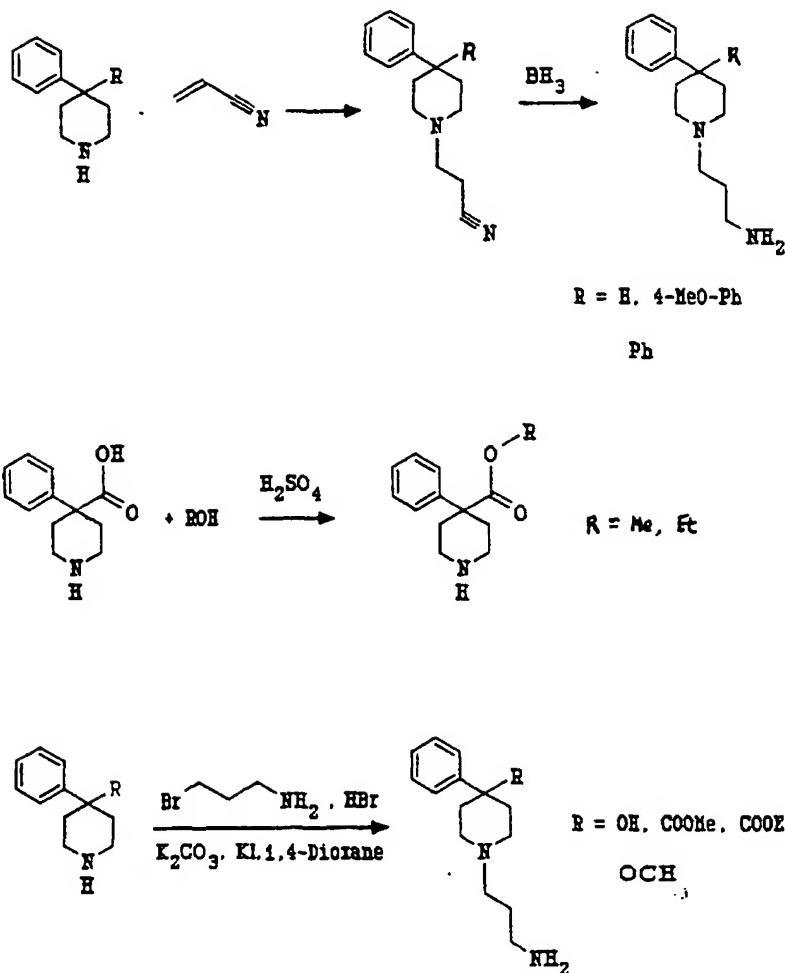
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Binding affinities of compounds 13-17 at cloned human $\alpha 1d$,
 $\alpha 1b$ and $\alpha 1a$ receptors.

5	Example	$\alpha 1d$			$\alpha 1b$			n	$\alpha 1a$			n
		pKi	SEM	n	pKi	SEM	n		pKi	SEM	n	
	13	6.14	0.02	3	6.21	0.09	3	9.74	0.02	3		
	14	6.46	0.04	3	6.59	0.08	3	9.68	0.05	3		
	15	6.01	0.03	3	6.33	0.06	3	9.41	0.09	3		
10	16	6.24	0.06	3	6.37	0.06	3	9.54	0.09	3		
	17	6.17	0.04	4	6.32	0.06	4	8.99	0.12	4		

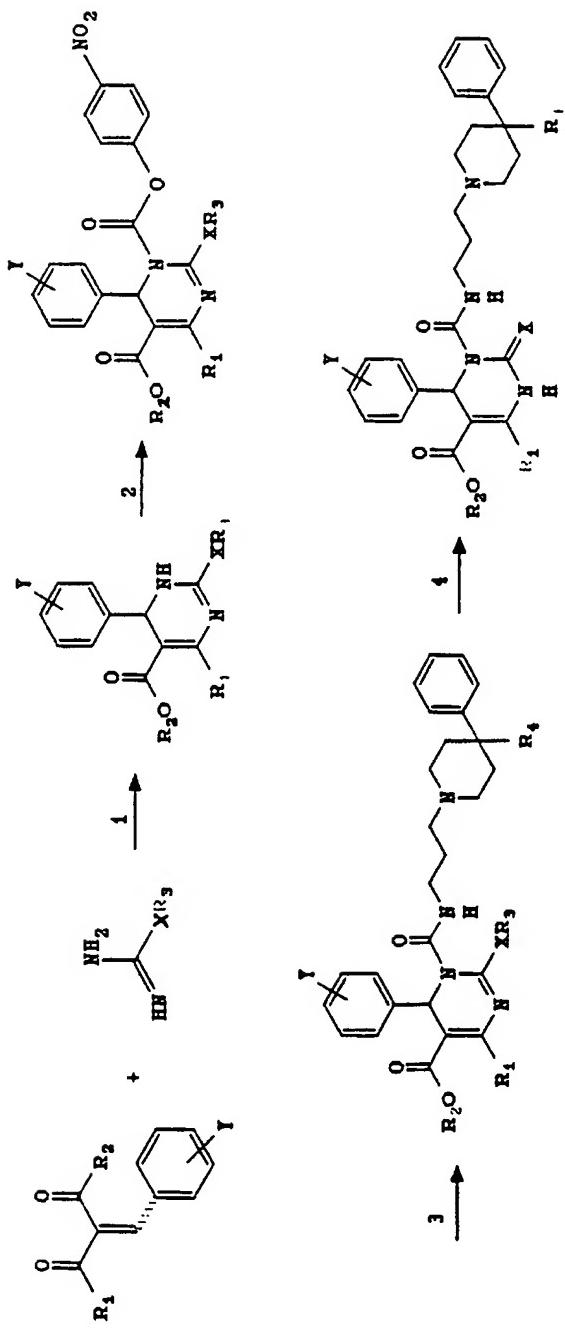
h = human

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Scheme 1. General synthetic schemes for the synthesis of the piperidine sidechains.

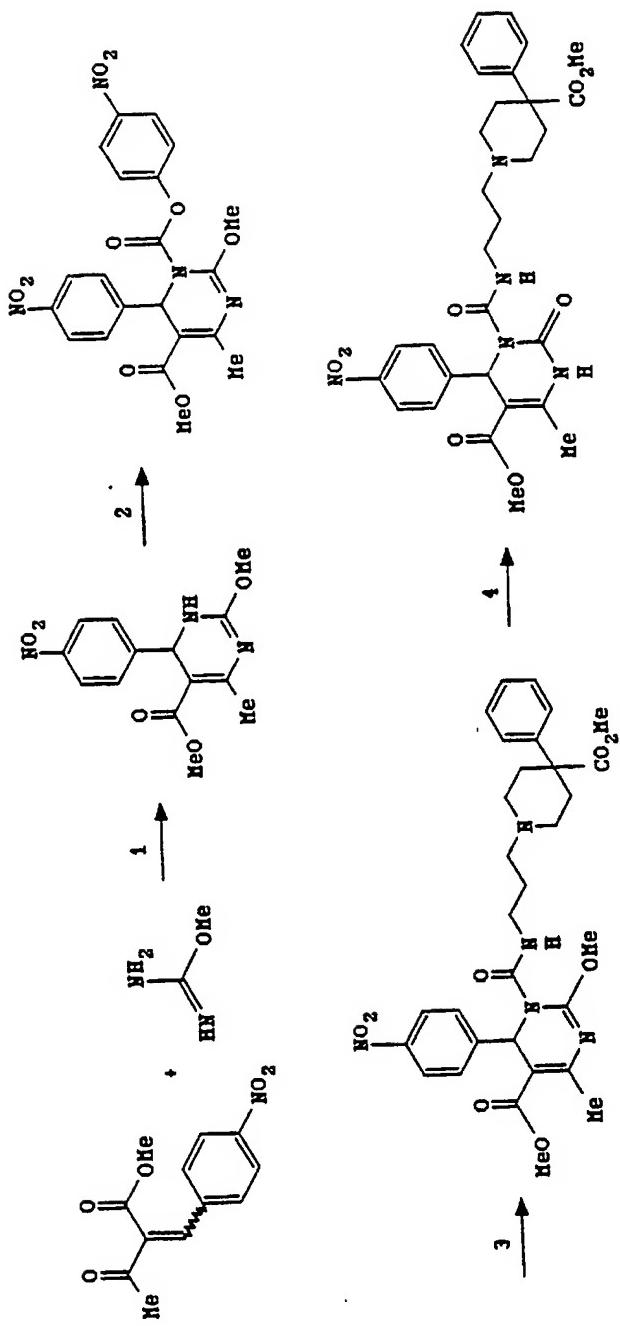
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1. NaOAc, DMF.
2. 4-Nitrophenyl chloroformate, NaHCO₃, CH₂Cl₂, H₂O.
- 3.
4. HCl/THF or EtSH/TFA.

Scheme 1 (continued). General synthetic scheme for examples 1-12.

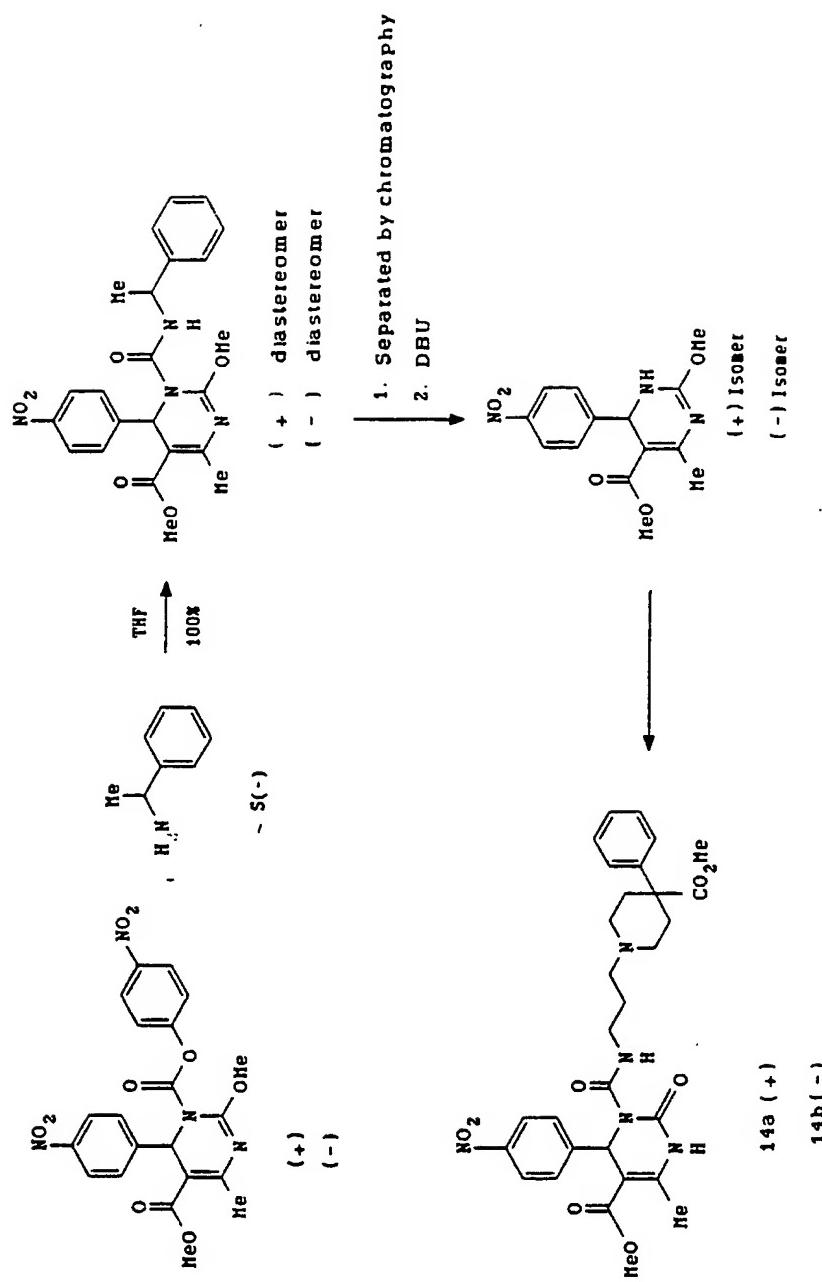
-202-



1. NaOAc, DMF.
2. 4-Nitrophenyl chloroformate, NaHCO₃, CH₂Cl₂, H₂O.
3. 3[(4-Methoxycarbonyl-4-phenyl)piperidine-1-yl]propylamine, THF.
4. 6N HCl/THF.

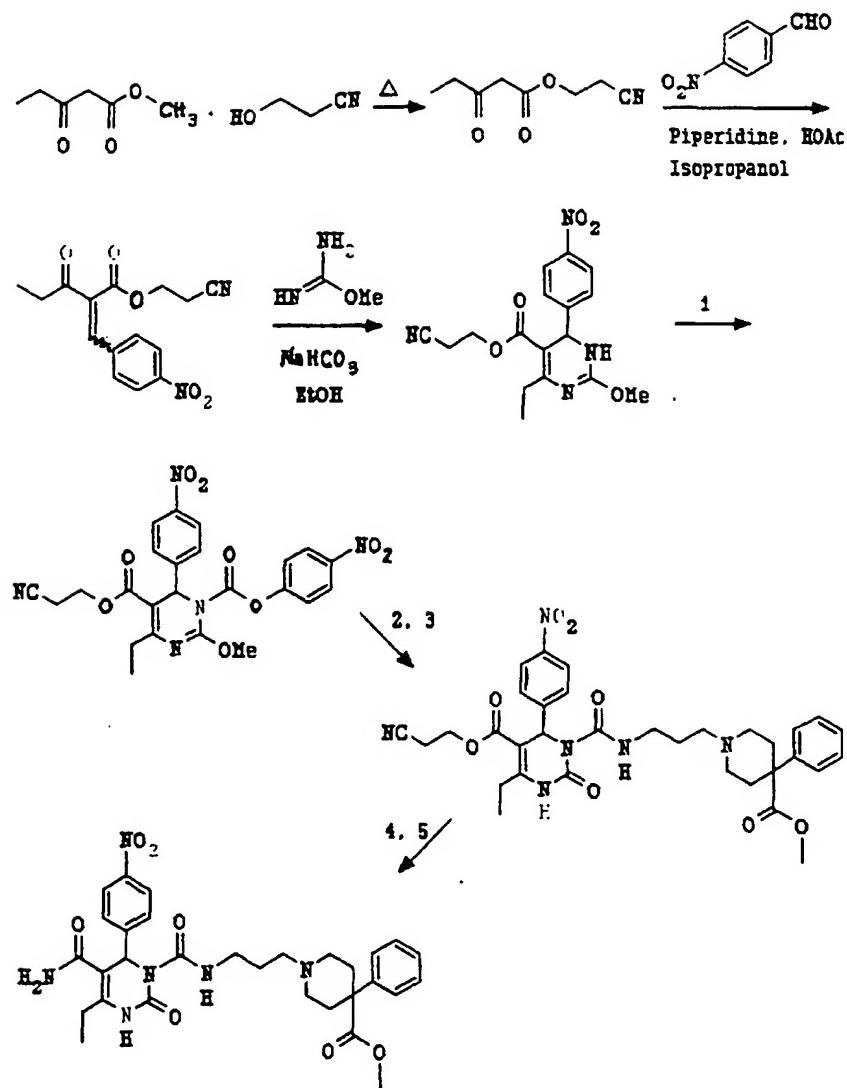
Scheme 2. Synthetic scheme for example 11.

-203-



Scheme 3. Synthetic scheme for examples 11a and 11b.

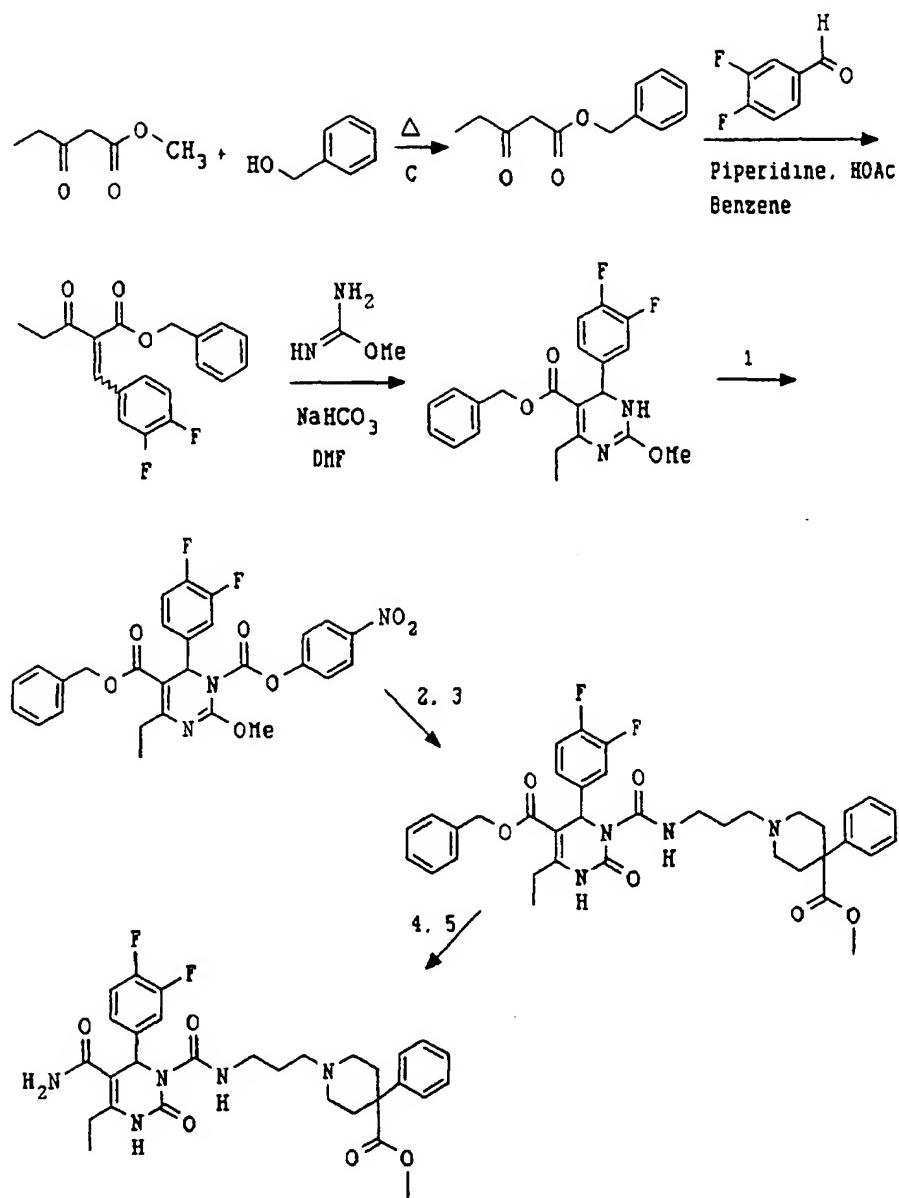
-204-



1. 4-Nitrophenyl chloroformate, NaHCO₃, CH₂Cl₂, H₂O.
2. 3 - [(4-Methoxycarbonyl-4-phenyl)piperidin-1-yl]propylamine.
3. 6N HCl.
4. NaOH, Acetone.
5. DMAPECD, DMAP, NH₃, CH₂Cl₂.

Scheme 4. Synthetic scheme for example 13.

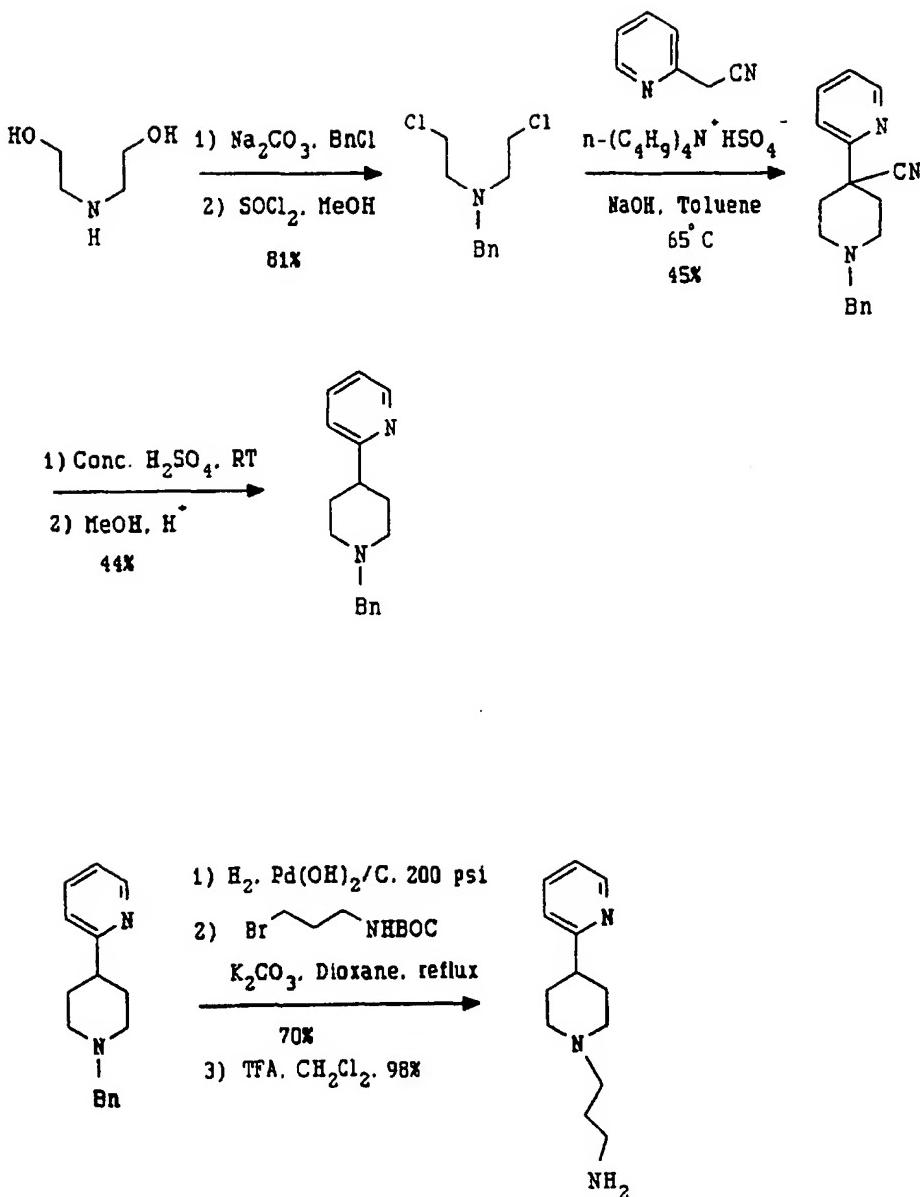
-205-



1. 4-Nitrophenyl chloroformate, DMAP, THF
2. 3-[(4-Methoxycarbonyl-4-phenyl)piperidin-1-yl]propylamine.
3. 6N HCl.
4. H₂, Pd-C, MeOH.
5. DMAPECD, DMAP, NH₄OH, CH₂Cl₂.

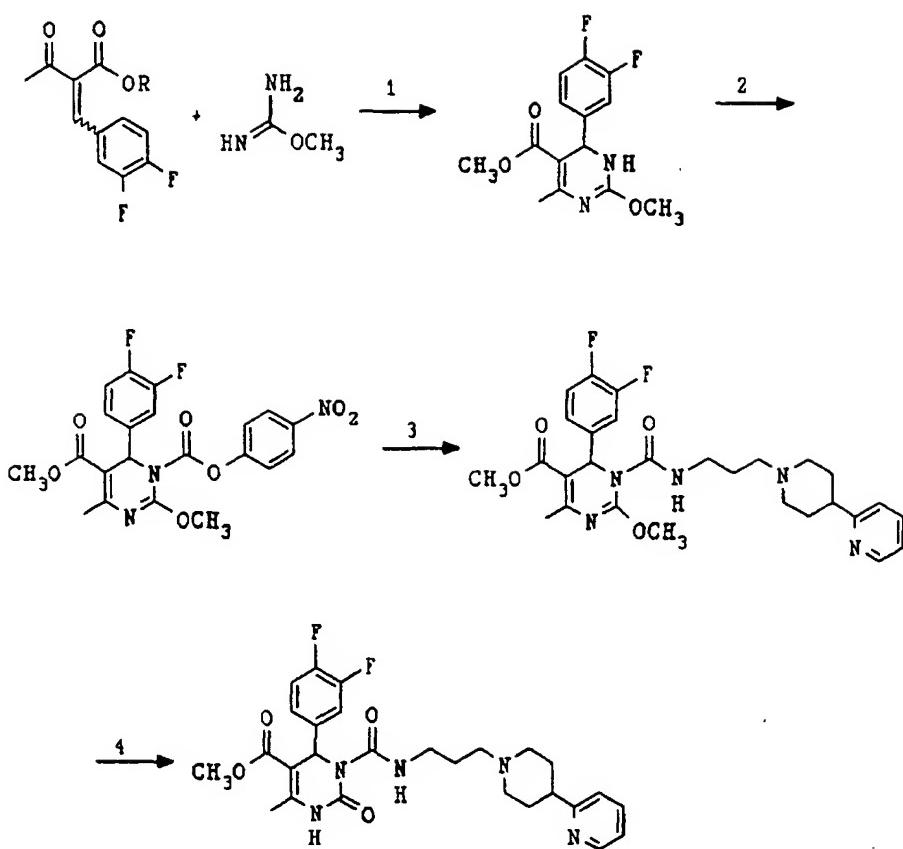
Scheme 5. Synthetic scheme for example 14.

-206-



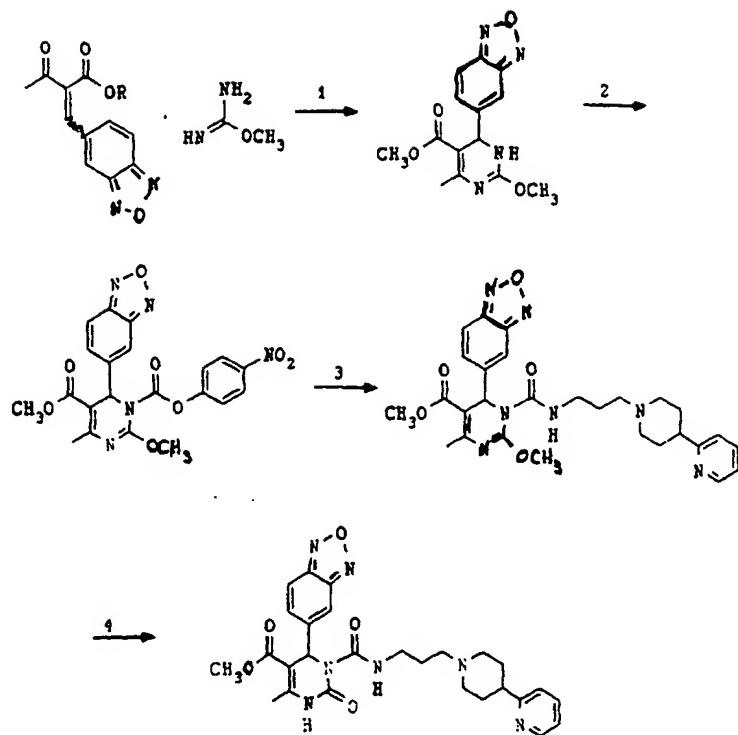
Scheme 6. Synthetic scheme for the preparation of 3-[4-(2-Pyridyl)-piperidin-1-yl]propylamine (Example 21 part d).

-207-



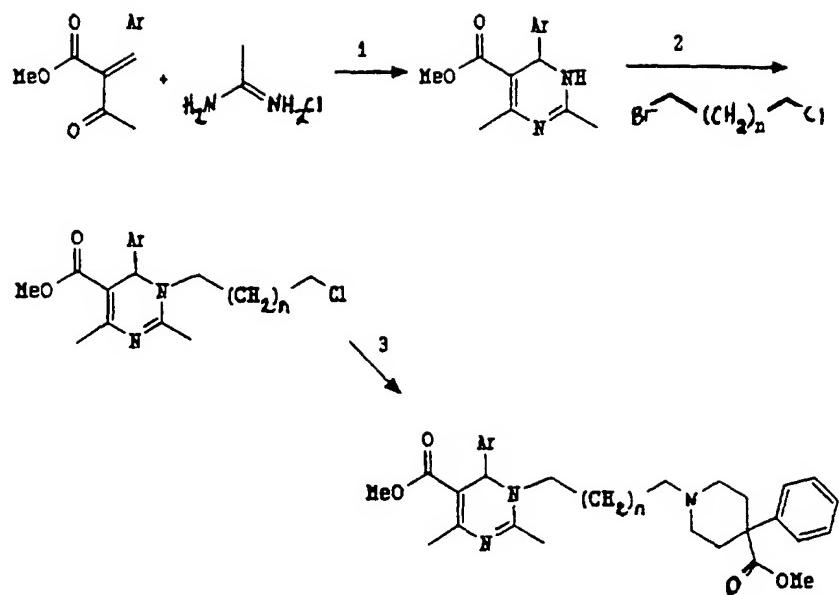
1. NaOAc, DMF.
2. 4-Nitrophenyl chloroformate, NaHCO₃, CH₂Cl₂, H₂O.
3. 3-[(4-Pyridyl)-piperidin-1-yl]propylamine, CH₂Cl₂.
4. 6N HCl/THF.

Scheme 7. Synthetic scheme for example 15.



1. NaOAc, DMF.
2. 4-Nitrophenyl chloroformate, NaHCO₃, CH₂Cl₂, H₂O.
3. 3-[(4-(2-Pyridyl)-piperidin-1-yl)propyl]amine, CH₂Cl₂.
4. 6N HCl/THF.

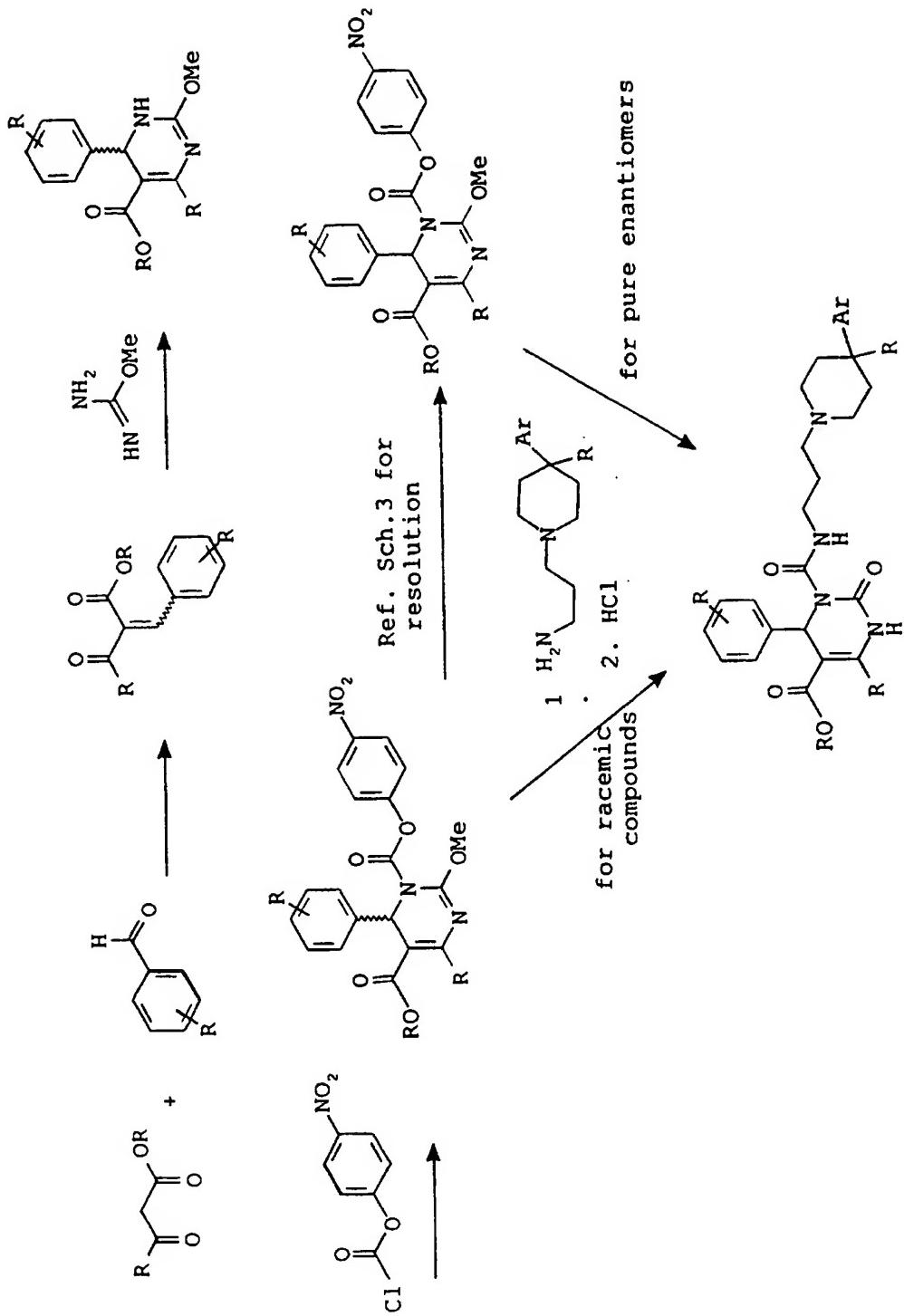
Scheme 8. Synthetic scheme for example 16.



1. (a) $t\text{-BuOK}$, DMF, 0°C ; (b) $\text{TsOH}\cdot\text{H}_2\text{O}$, DMF, $100\text{--}120^\circ\text{C}$.
2. NaH , THF, reflux.
3. 4-Methoxycarbonyl-4-phenylpiperidine, K_2CO_3 , NaI , 1,4-dioxane, reflux.

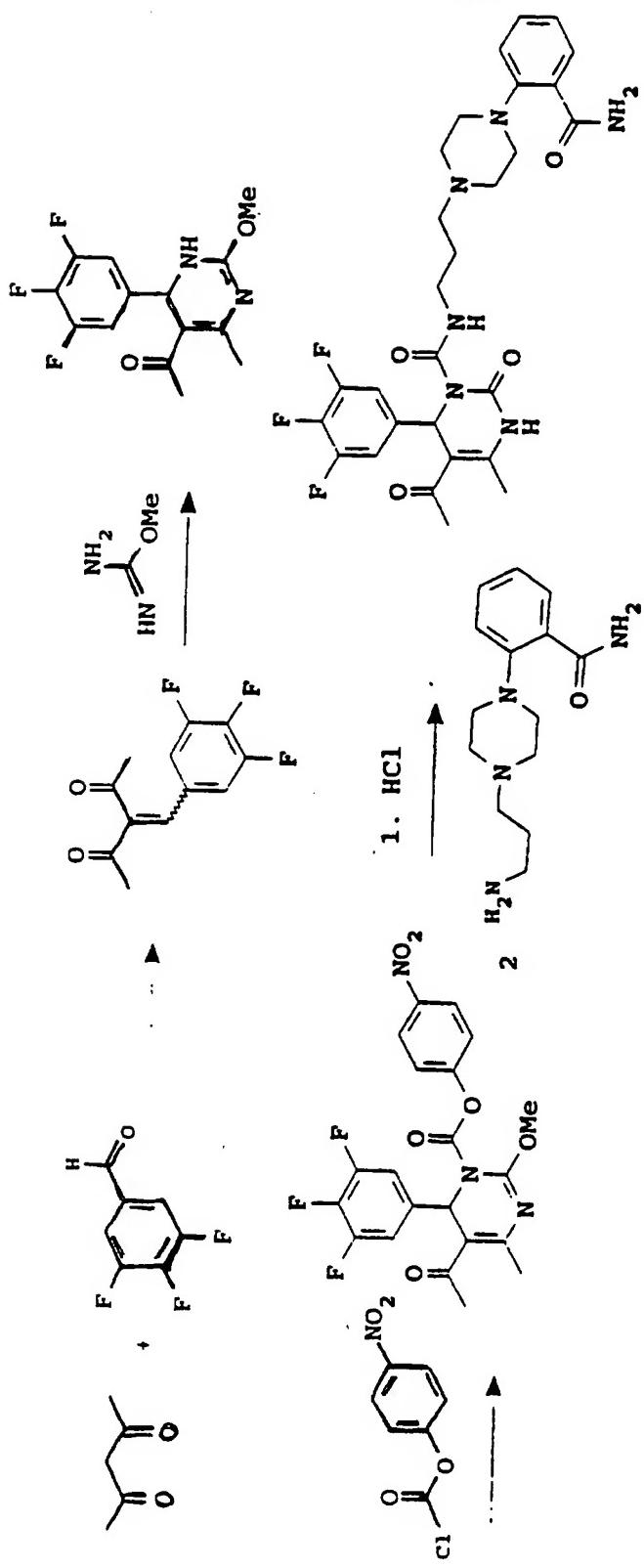
Scheme 9. Synthetic scheme for example 17.

-210-



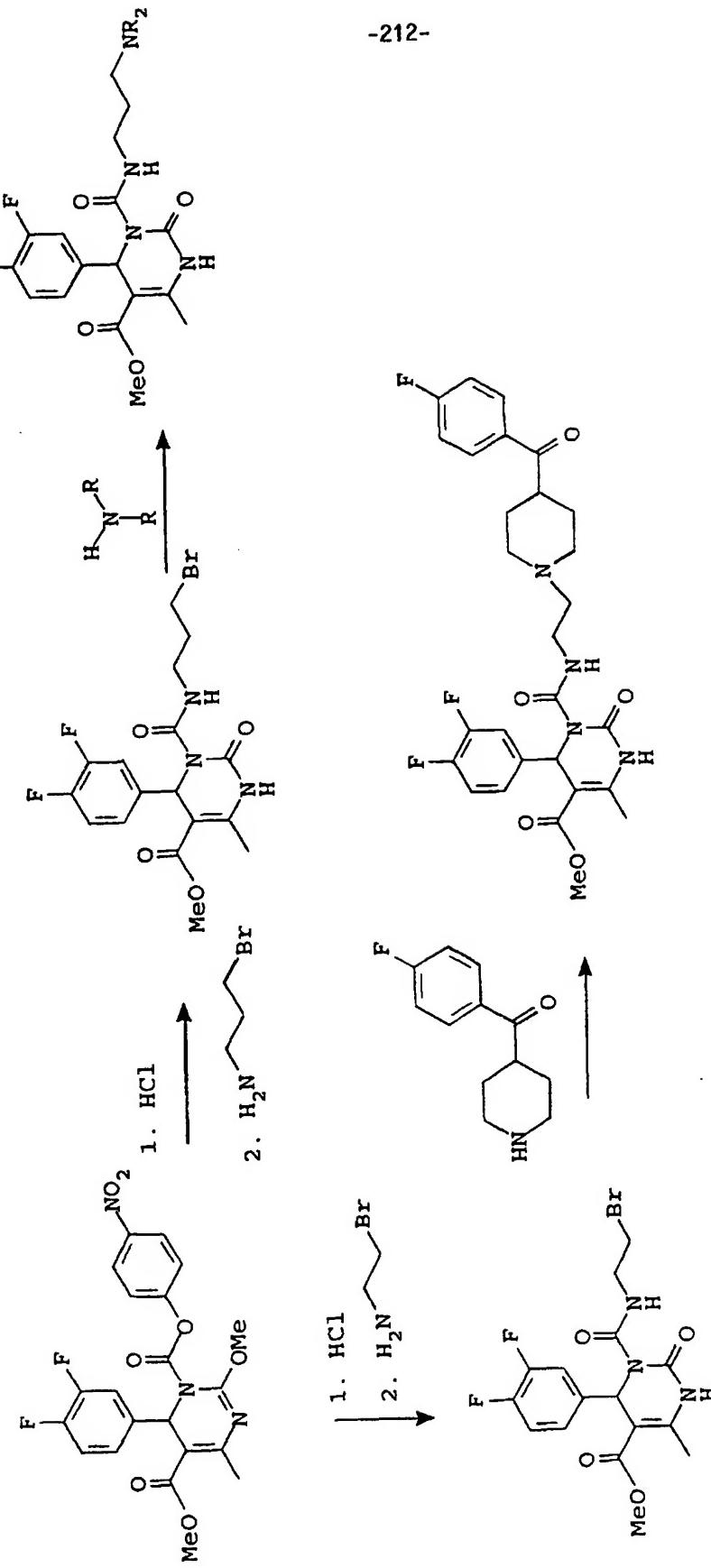
Scheme 10. General synthetic scheme for examples 18, 41, 42, 43, 44, and 45.

-211-



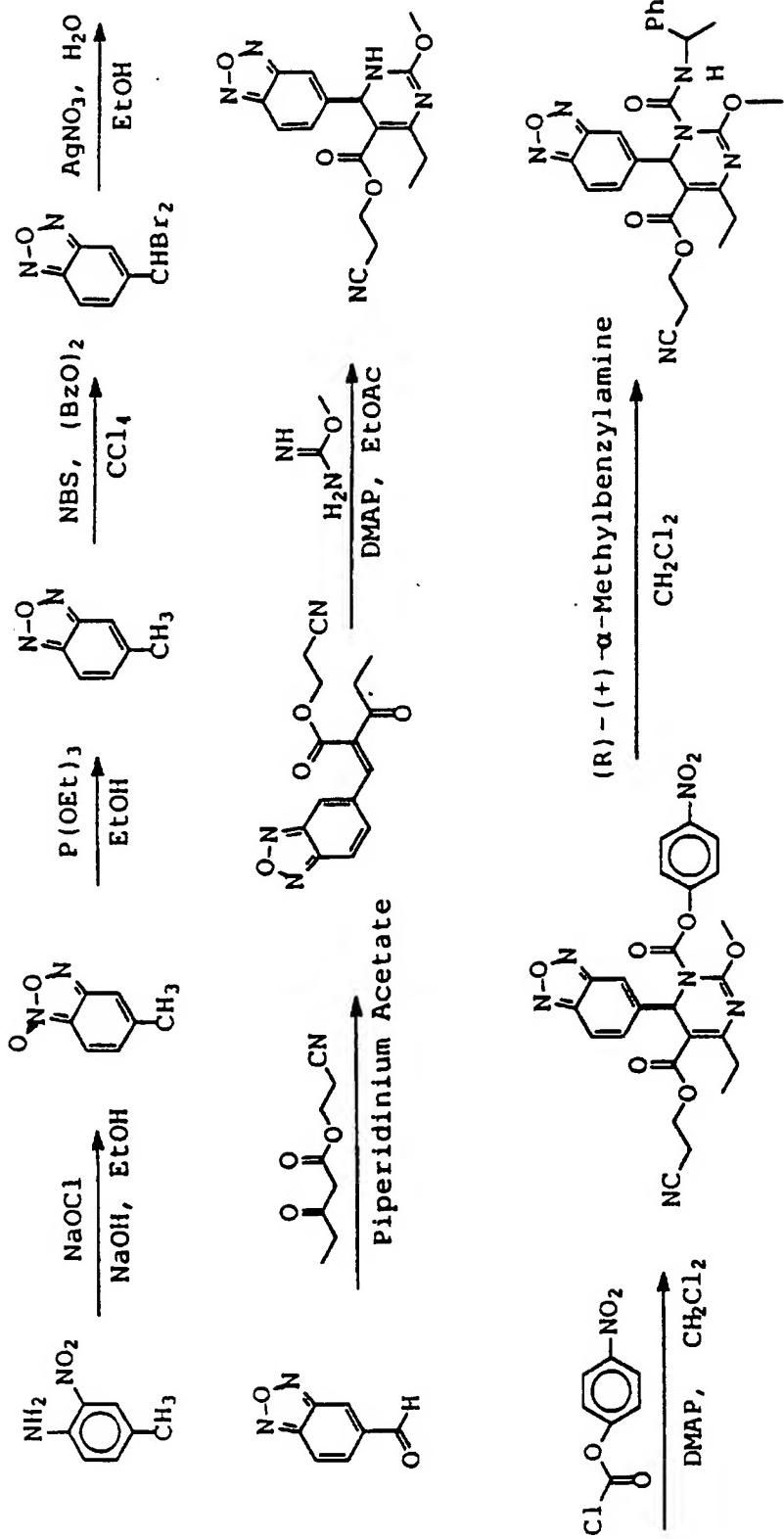
Scheme 11. Preparation of example 29.

-212-



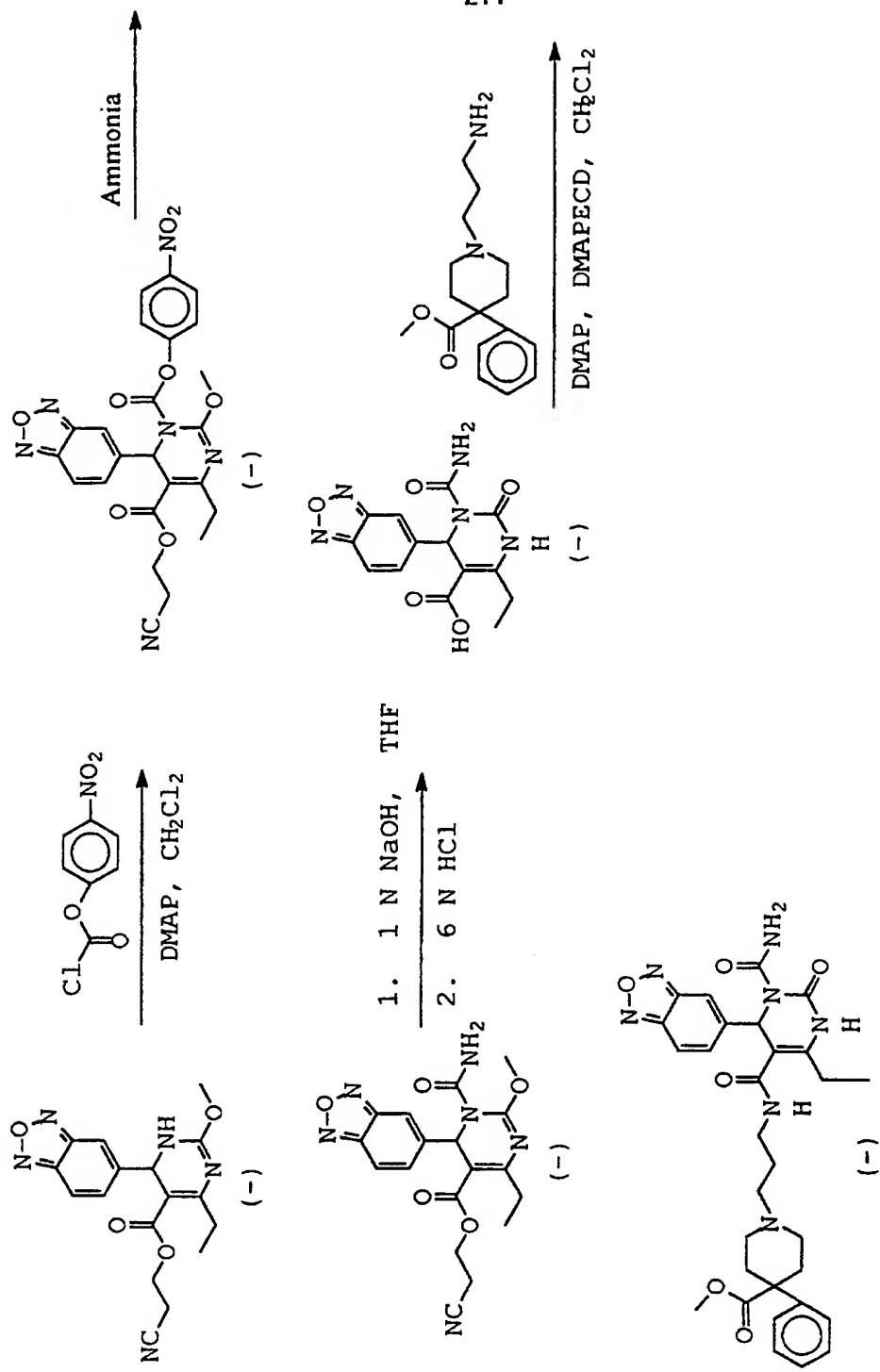
Scheme 12. General synthetic scheme for examples 30, 31, 35, 37, 39, 40, 47 and 48.

-213-

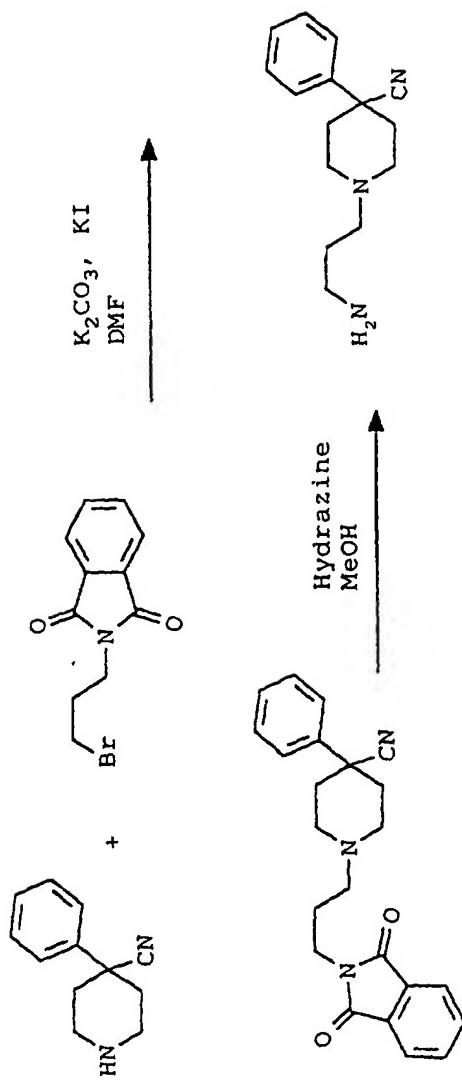


Scheme 13. Preparation of example 37 part-1

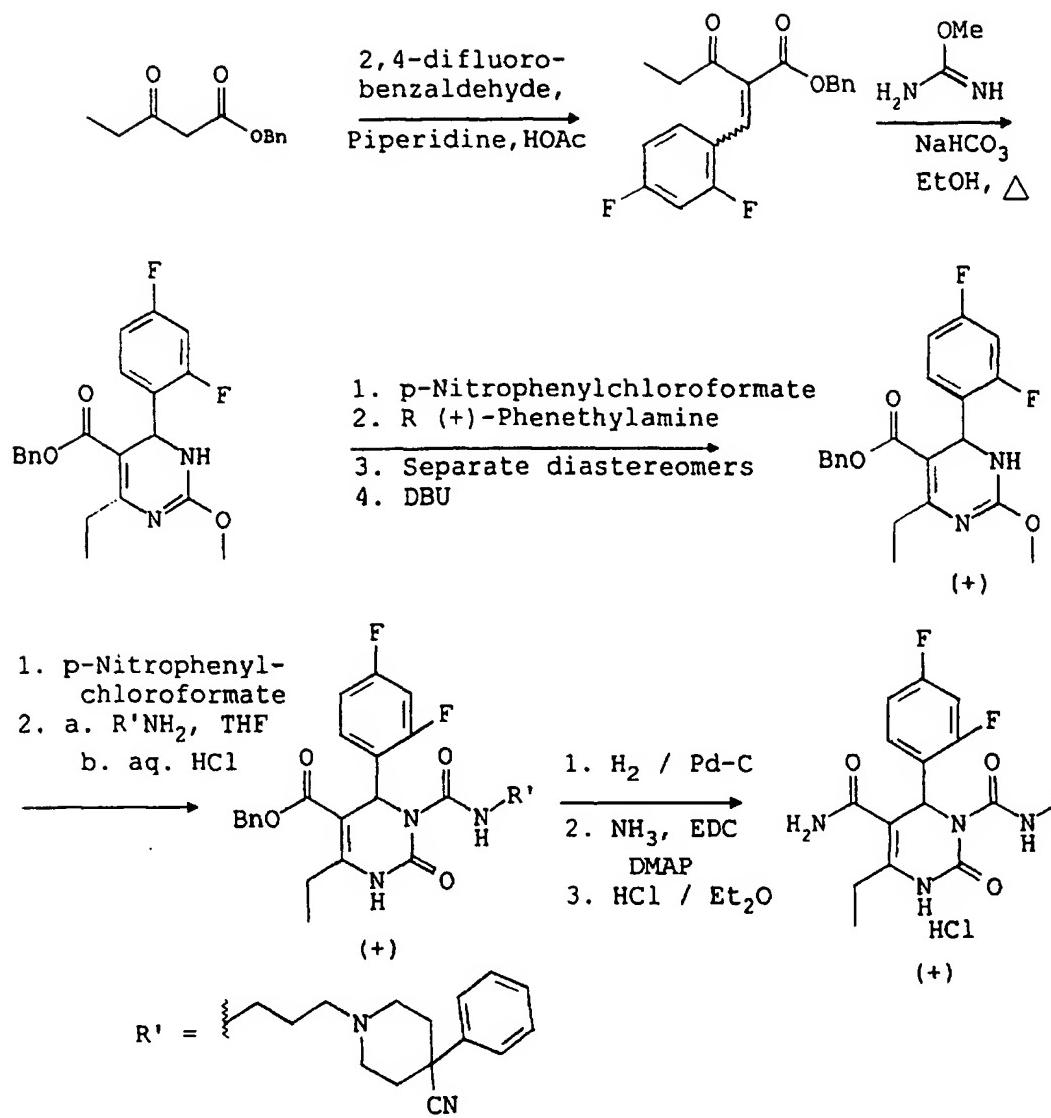
-214-



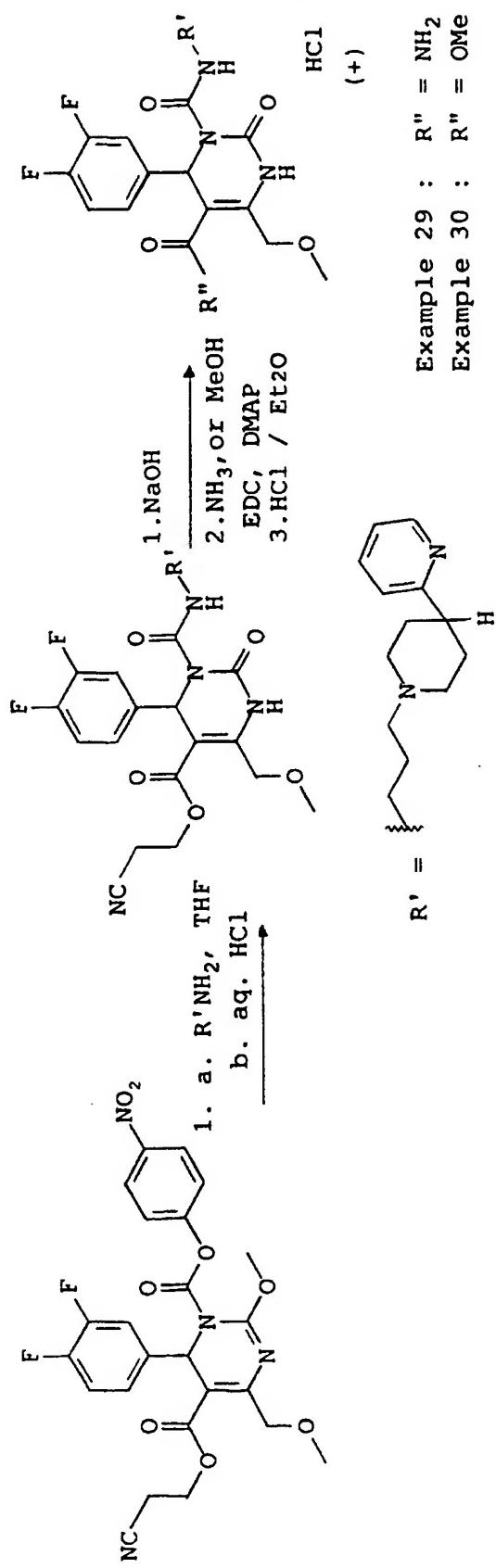
Scheme 13 (continued). Preparation of example 37 part-2



Scheme 14. Preparation of example 22 (part -1)

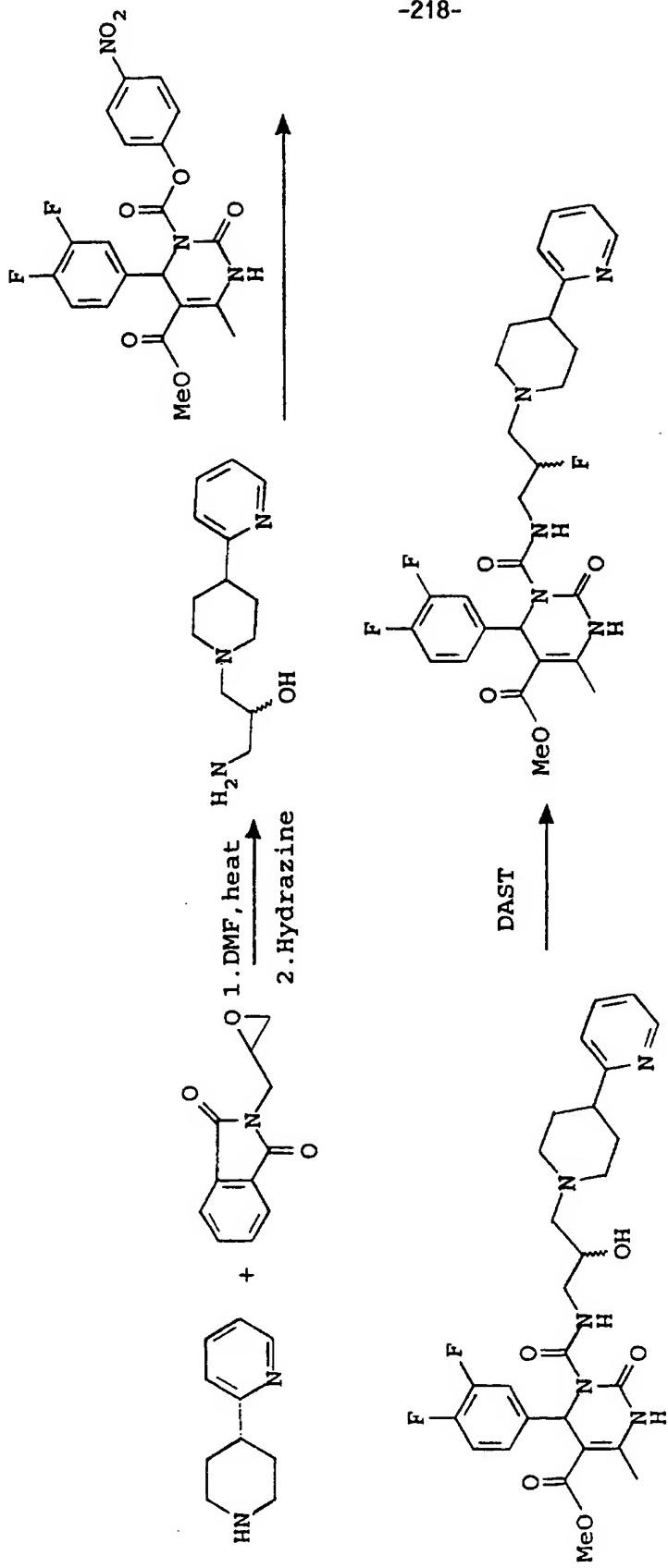


Scheme 14 (cont.). Preparation of example 22 (part-2)



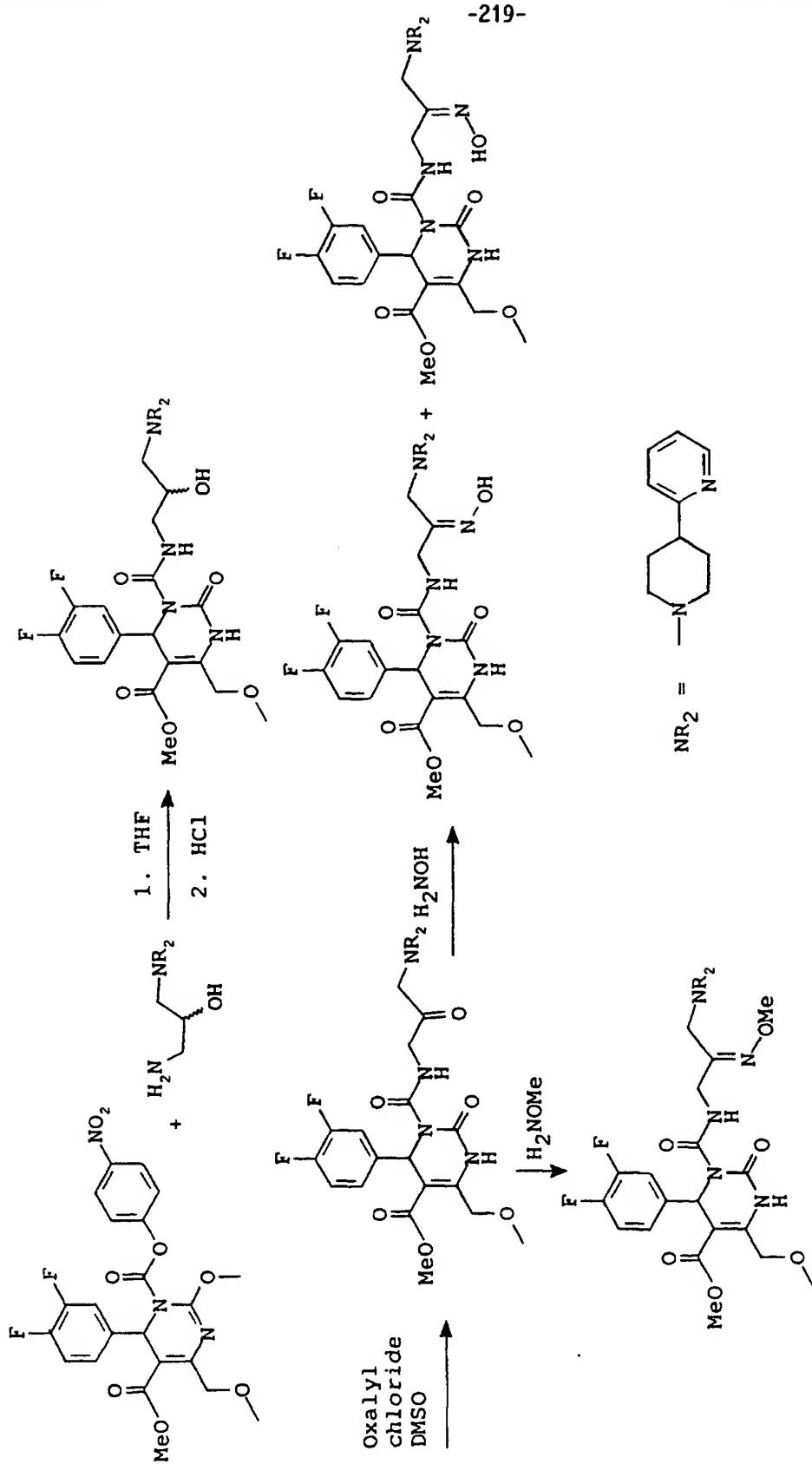
Scheme 15. Preparation of examples 23 and 24.

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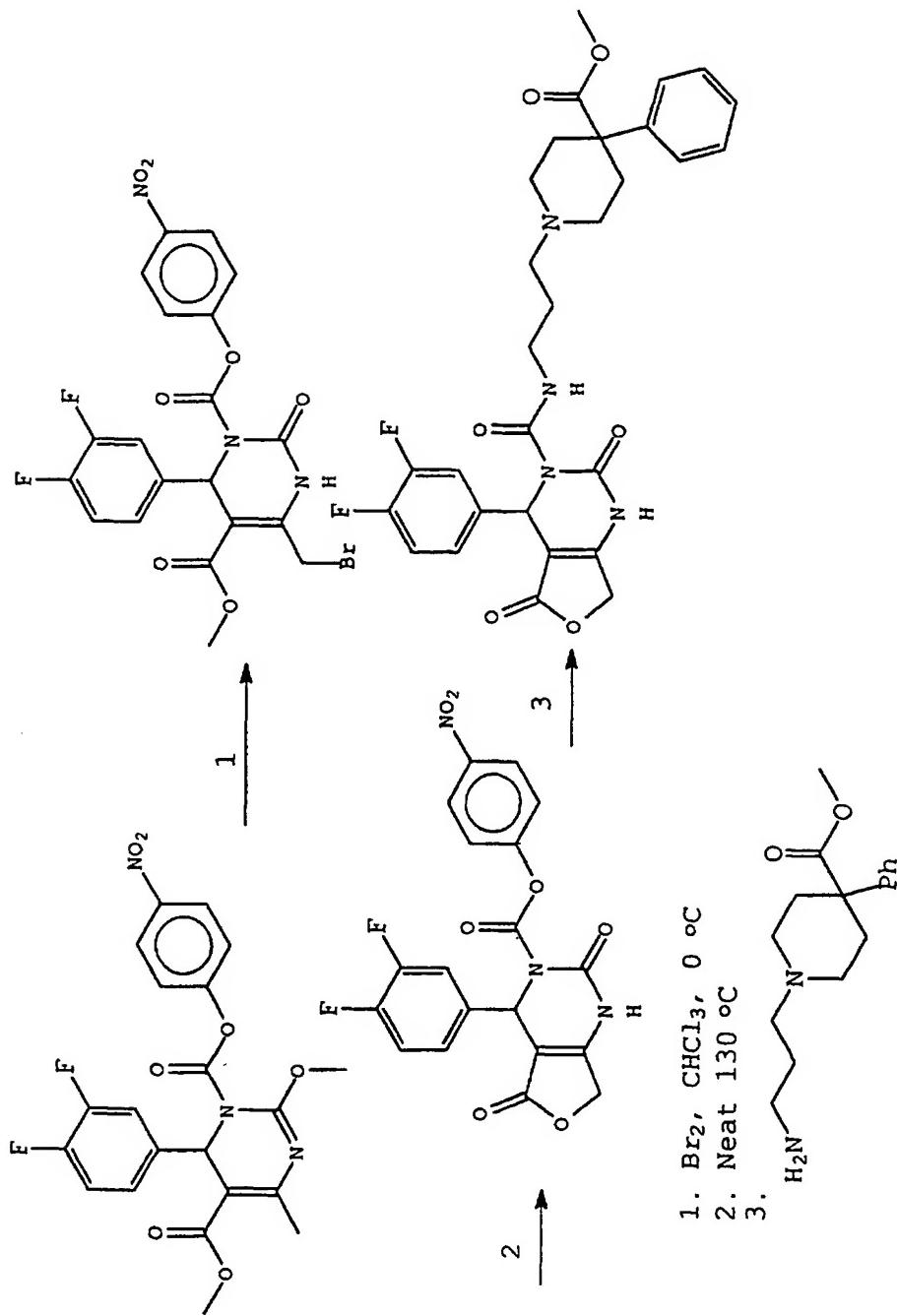
Scheme 16. Preparation of examples 19, 20 and 21.

-219-



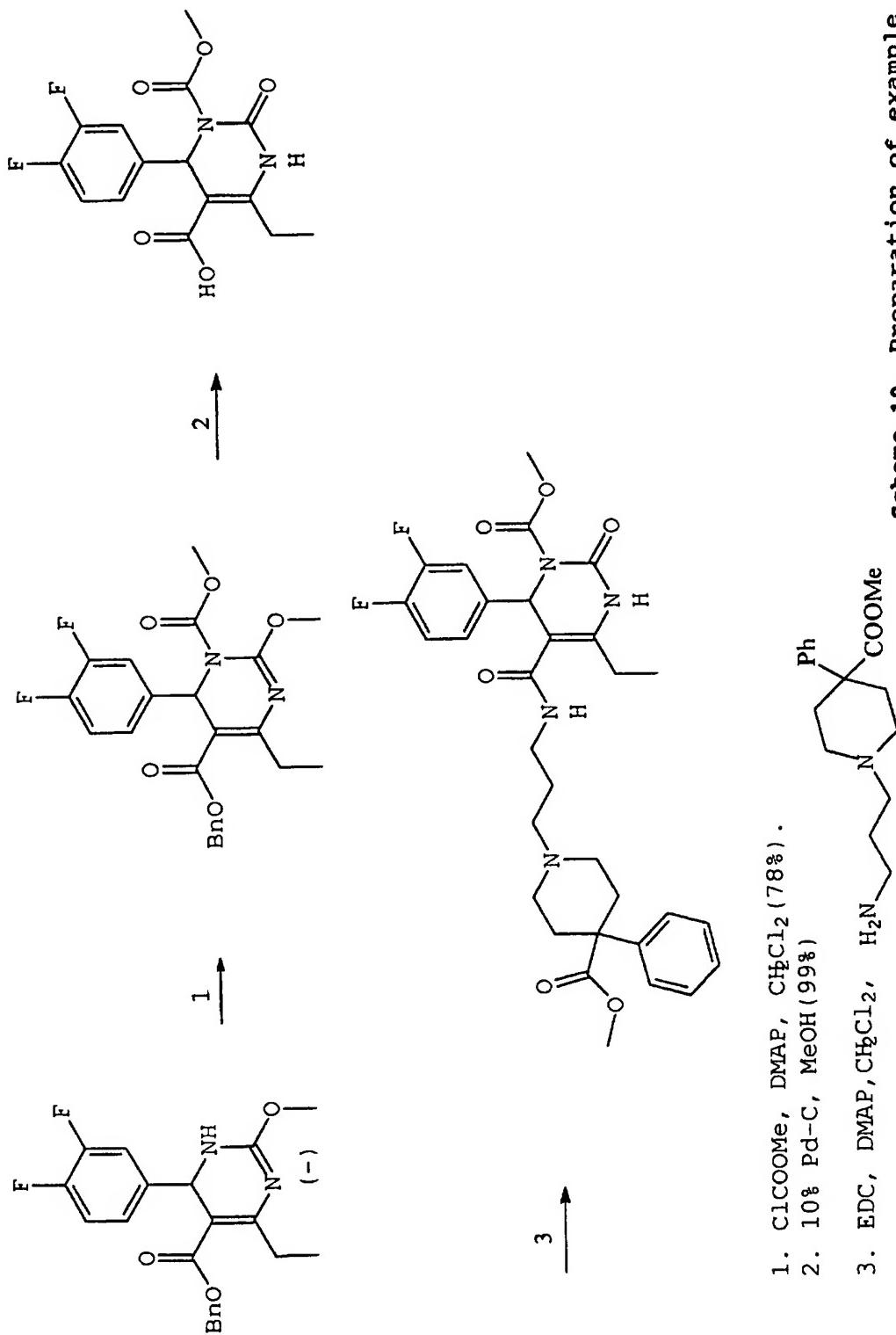
Scheme 17. Preparation of examples 25, 26, 27 and 28.

-220-



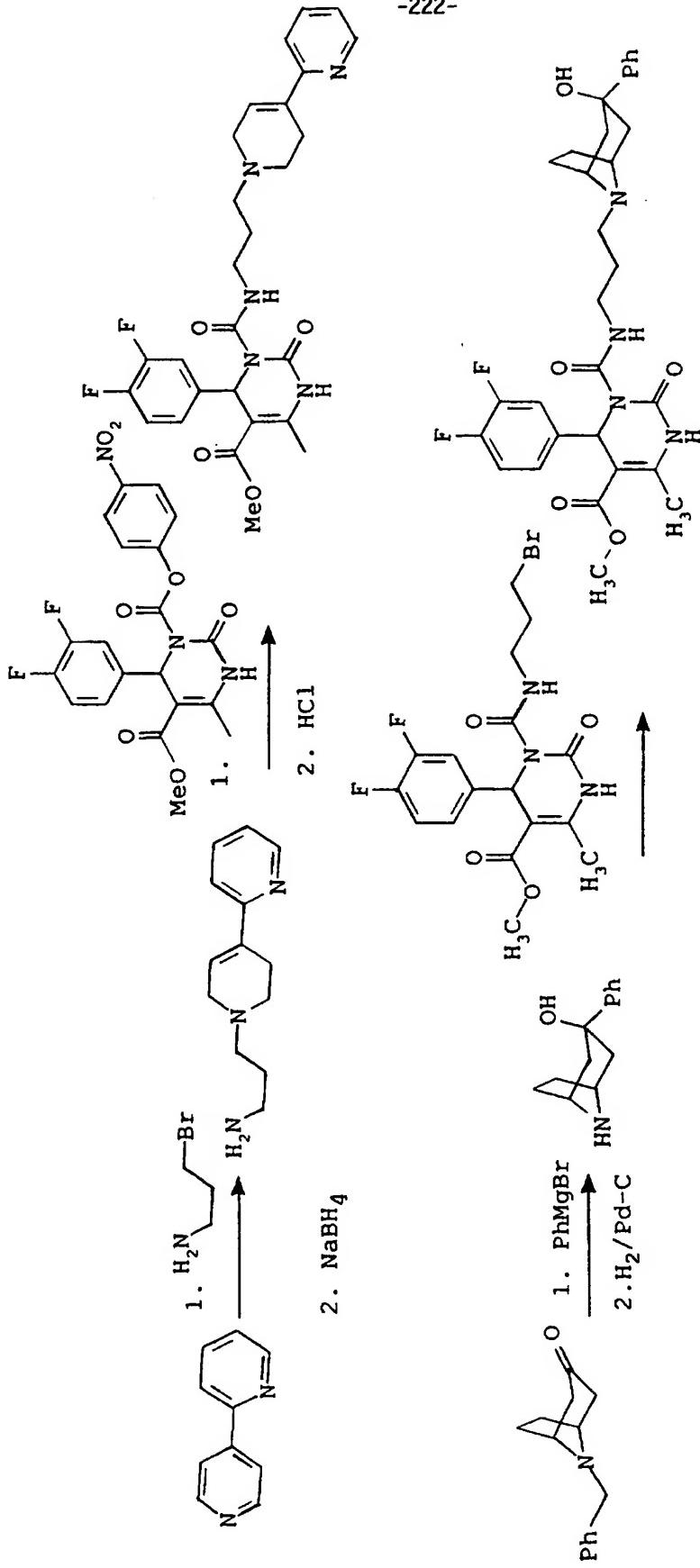
Scheme 18. Preparation of examples 33 and 34.

-221-



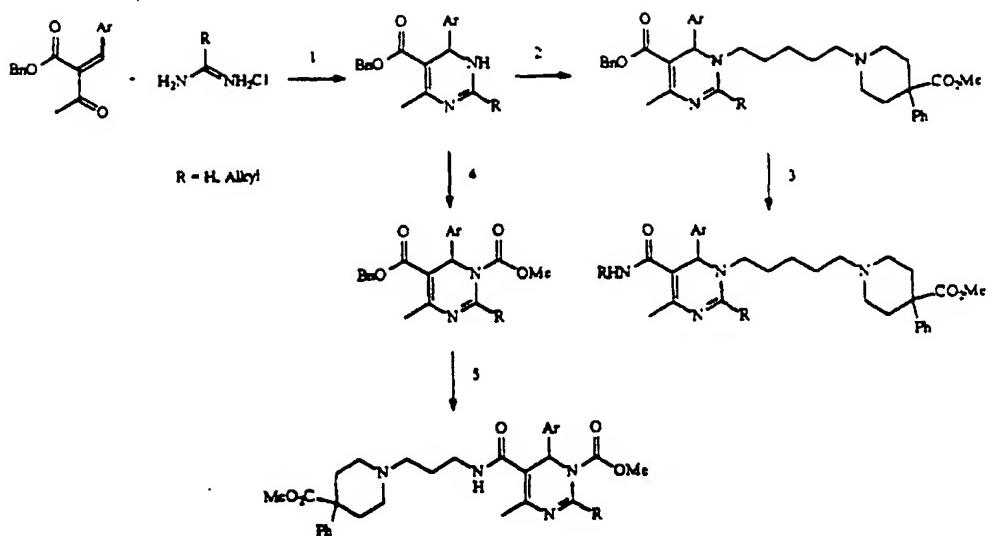
Scheme 19. Preparation of example 32.

-222-



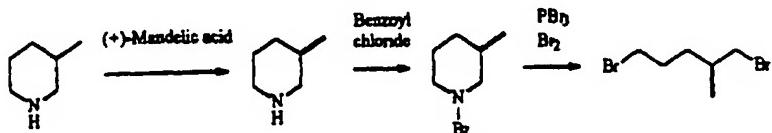
Scheme 20. Preparation of examples 38 and 46.

- 223 -



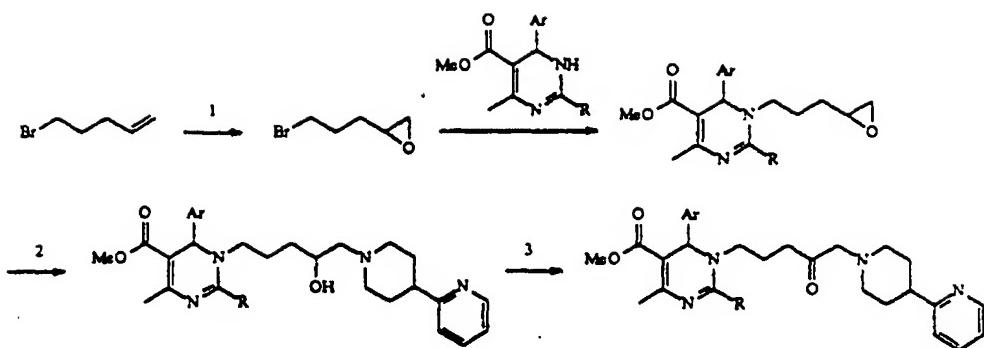
1. (a) KtBuO , DMF; (b) $\text{TsOH}\cdot\text{H}_2\text{O}$, DMF, 100-110°C.
2. (a) NaH , THF, 1,5-dibromopentane; (b) 4-Methoxycarbonyl-4-phenylpiperidine, K_2CO_3 , dioxane.
3. (a) H_2 , Pd/C , MeOH . (b) CH_3NH_2 , DMAPECD, CH_2Cl_2 .
4. NaH , ClCO_2Me , THF.
5. (a) H_2 , Pd/C , MeOH . (b) 3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine, DMAPECD, CH_2Cl_2 .

Scheme 21 (part-2). Synthetic scheme for examples 49, 50 and 51.



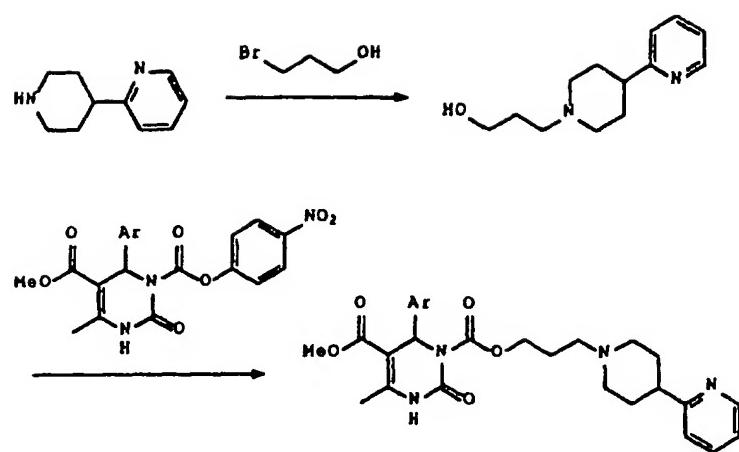
Scheme 21 (part-1). Synthesis of (S)-(-)-2-methyl-1,5-dibromopentane (Thurkauf et al. J. Org. Chem. 1987, 52, 5466-5467).

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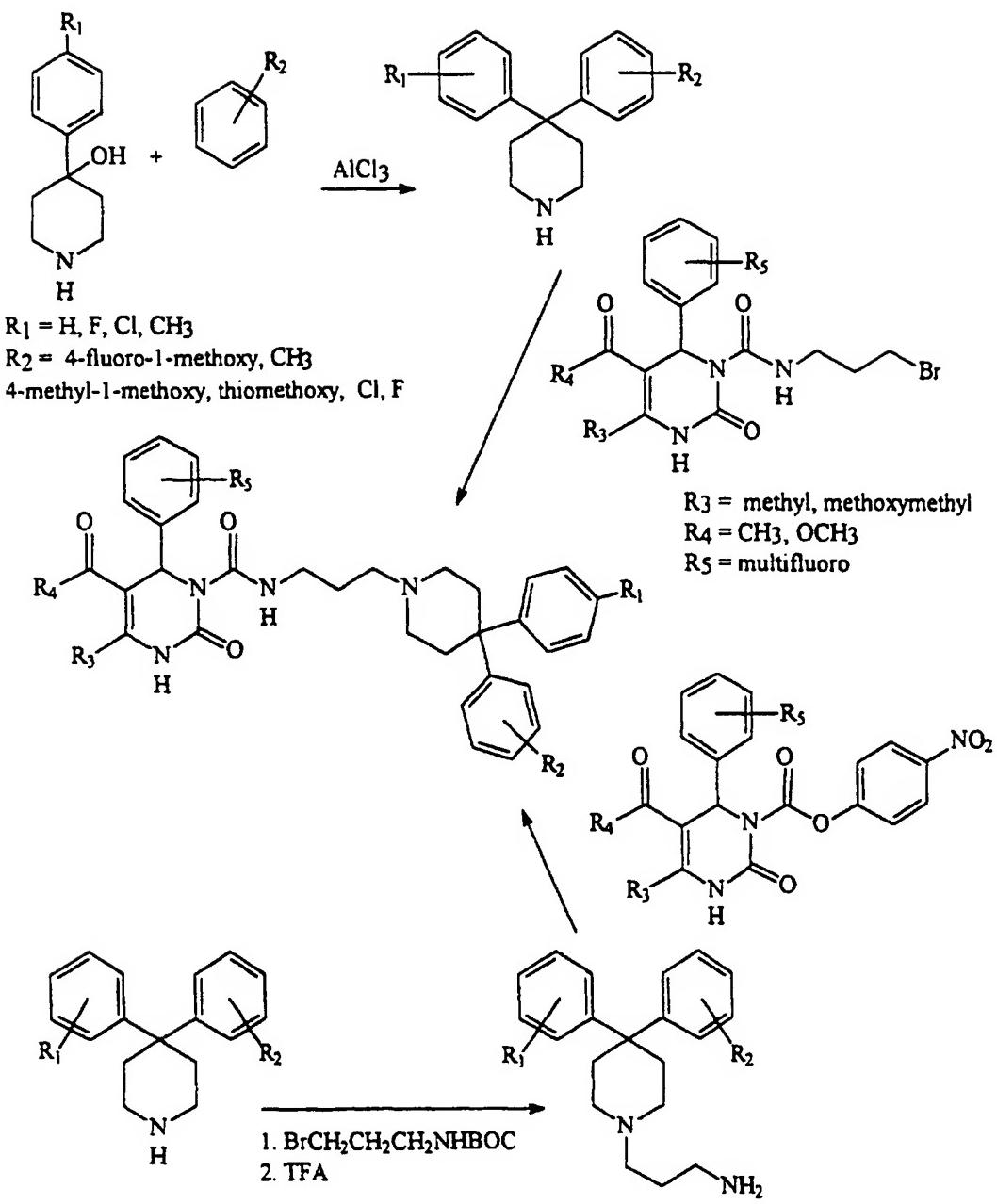


1. mCPBA, CH_2Cl_2 .
2. 4-(2-Pyridyl)piperidine, dioxane.
3. Oxalyl chloride, DMSO, CH_2Cl_2 .

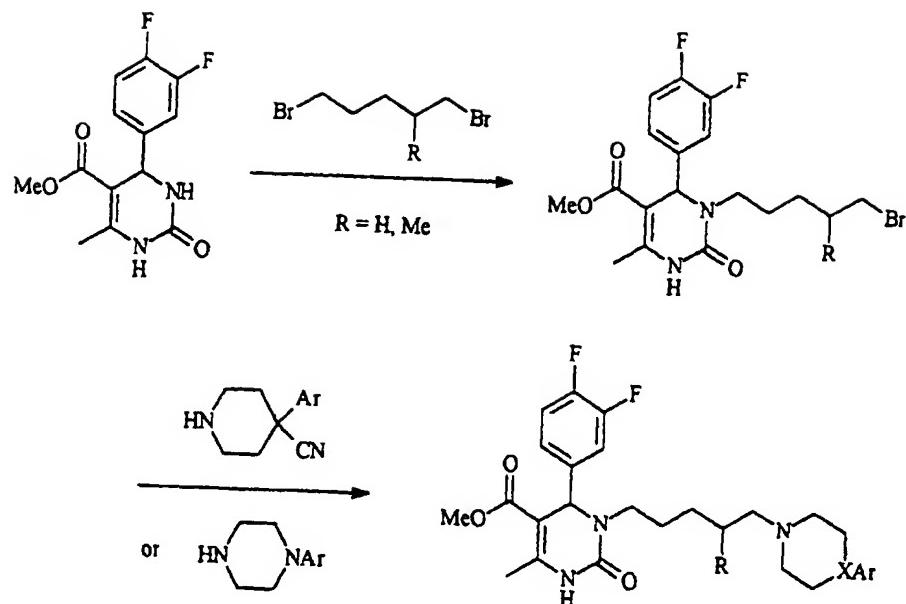
Scheme 22. Synthetic scheme for examples 56 and 57



Scheme 23. Synthetic scheme for example 59



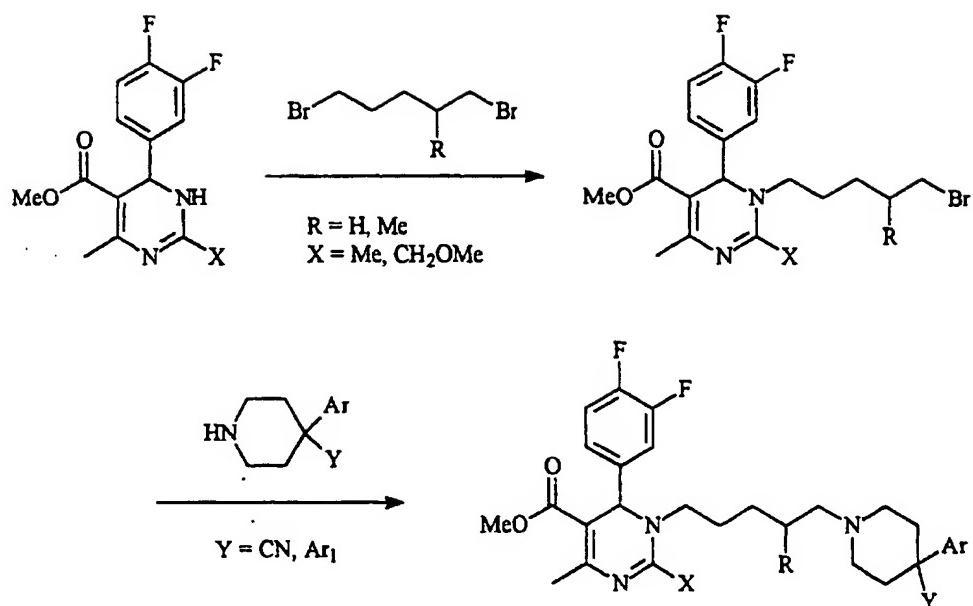
Scheme for the synthesis of examples 61-67.



Synthetic scheme for examples 68 and 69.

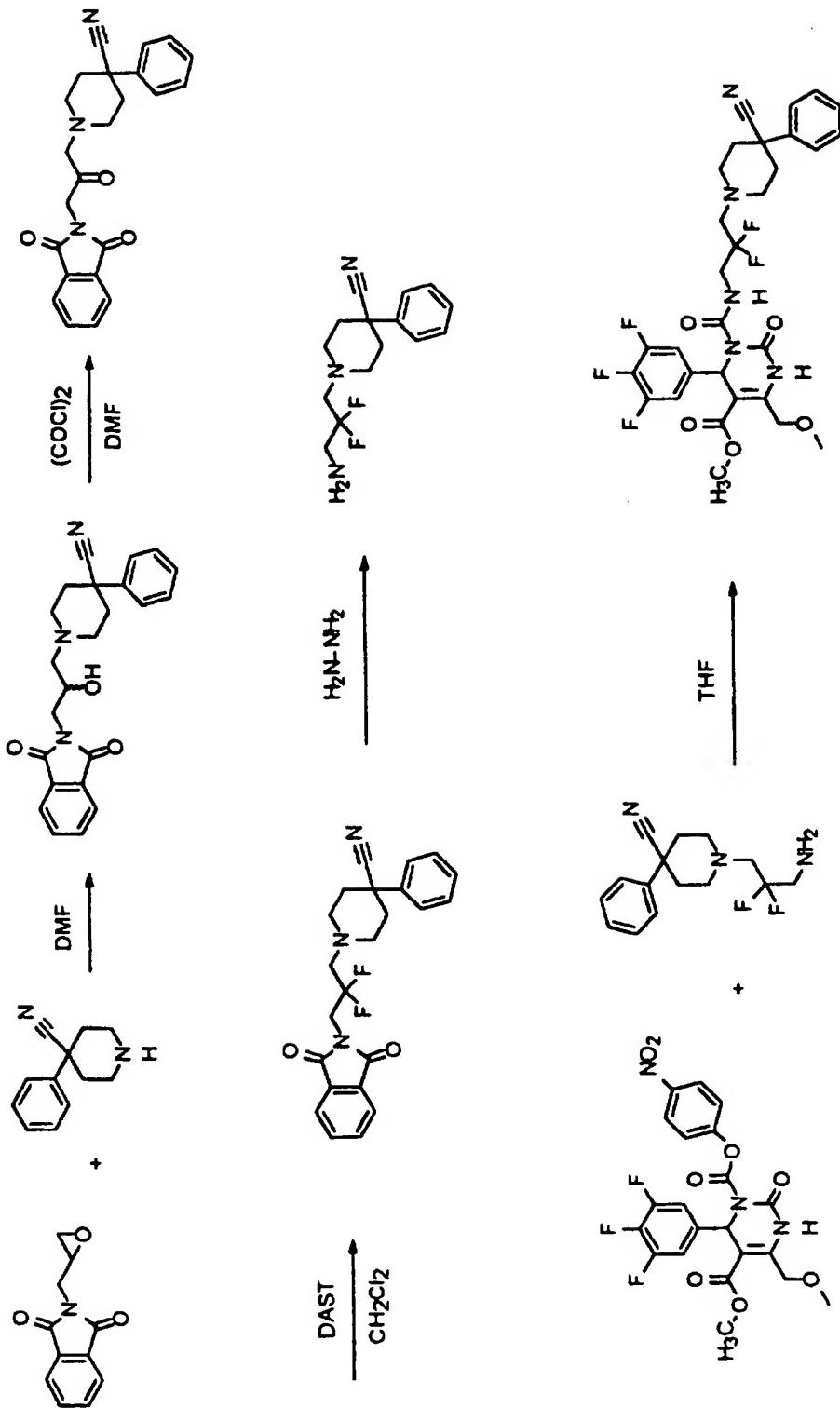
$X = \text{N}, \text{C}-\text{CN}$

-228-



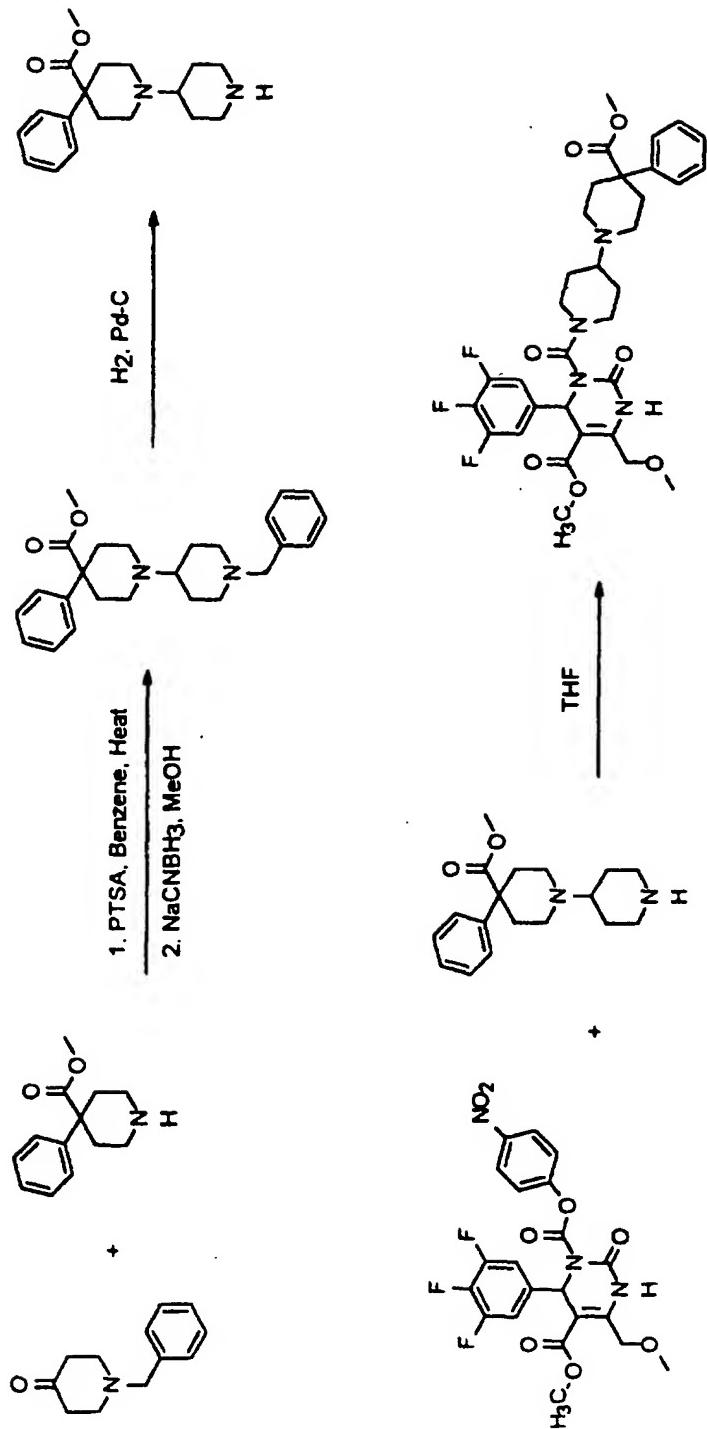
Synthetic scheme for examples 70–72.

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Scheme for the synthesis of example 76.

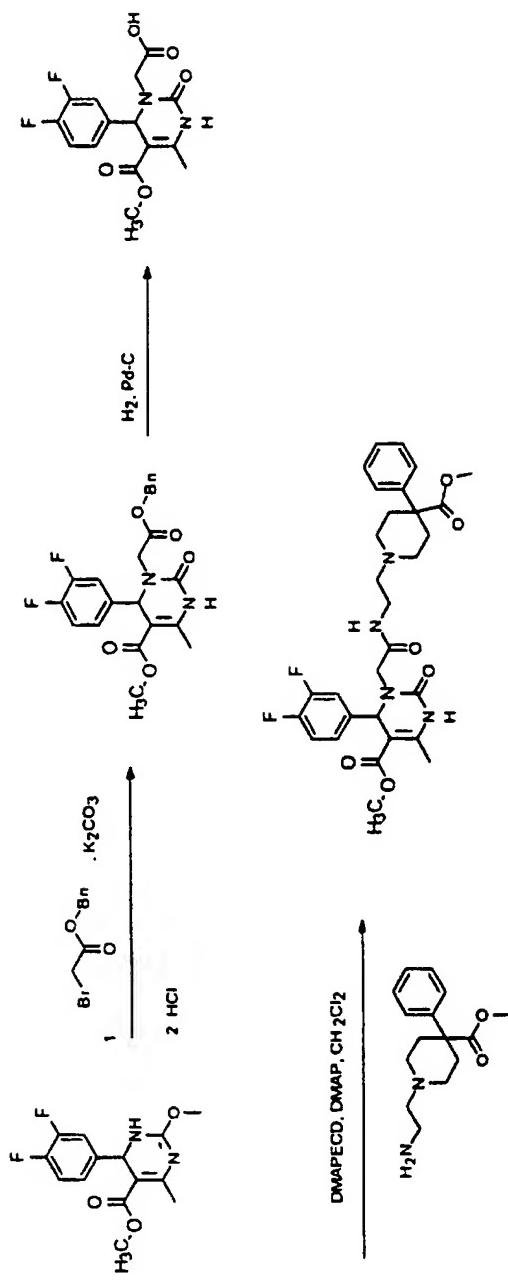
-230-



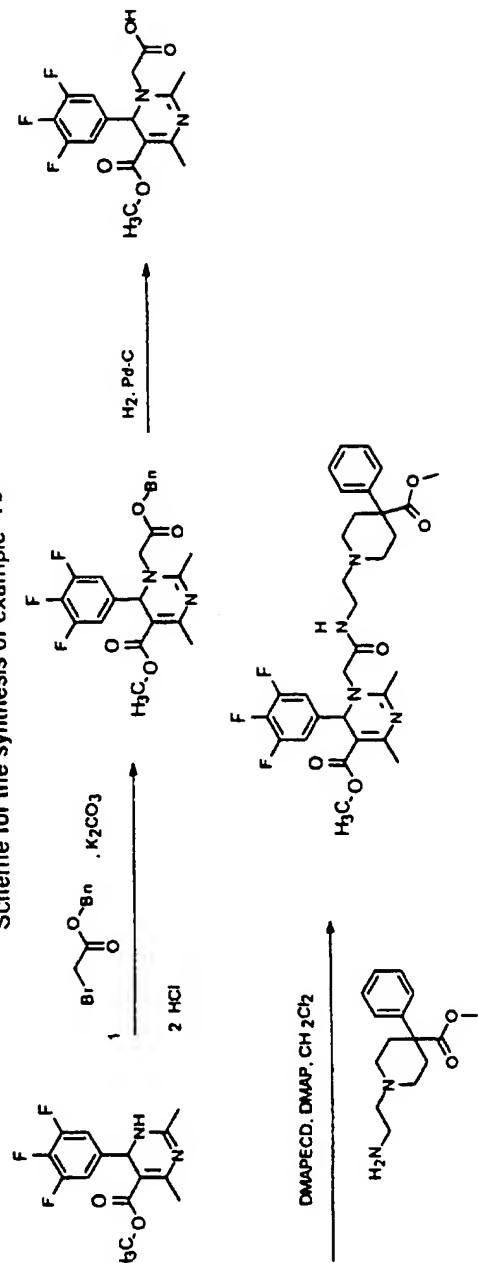
Scheme for the synthesis of example 77.

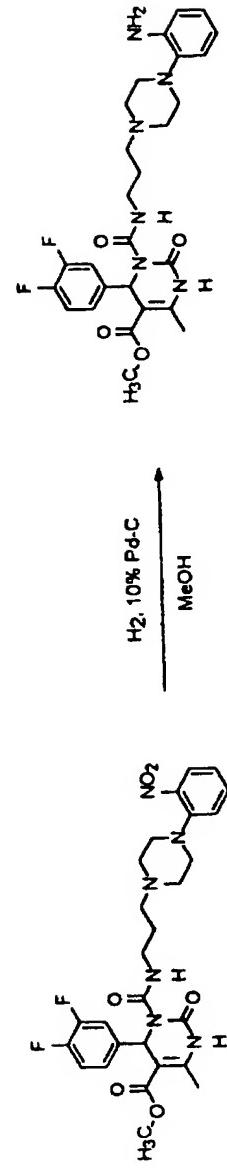
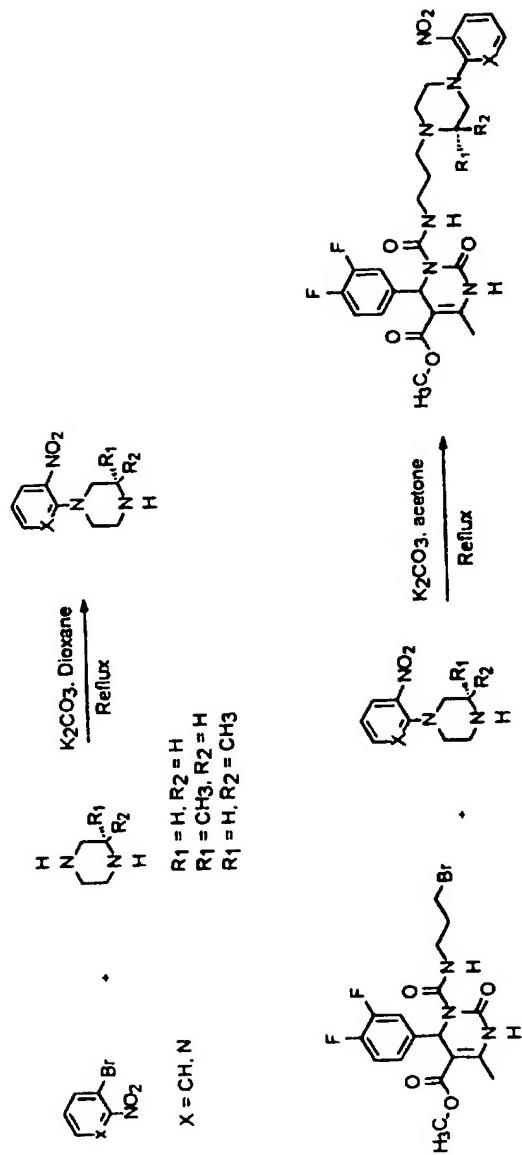
-231-

Scheme for the synthesis of example 78



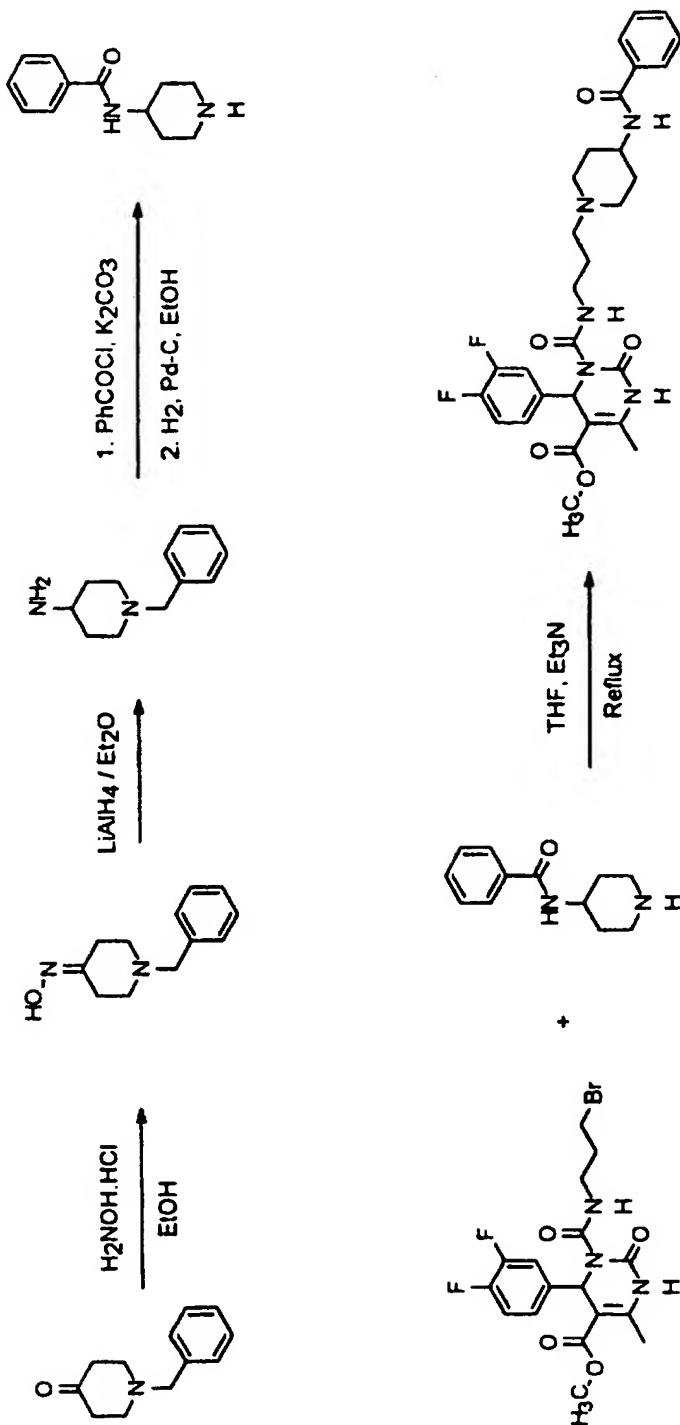
Scheme for the synthesis of example 79





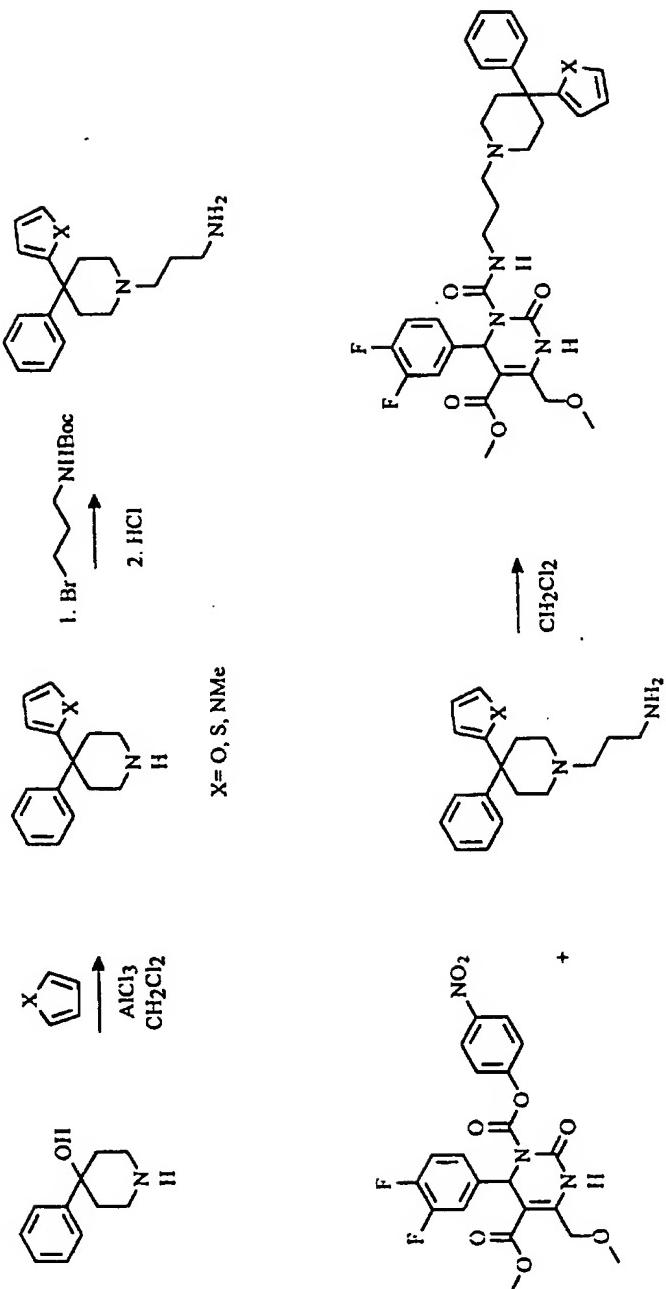
Scheme for the synthesis of examples 80, 82, 83 and 84.

Scheme for the synthesis of example 81.



Scheme for the synthesis of example 88.

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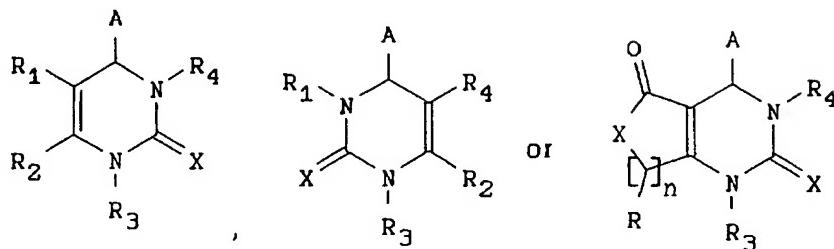


Synthetic scheme for examples 89-91.

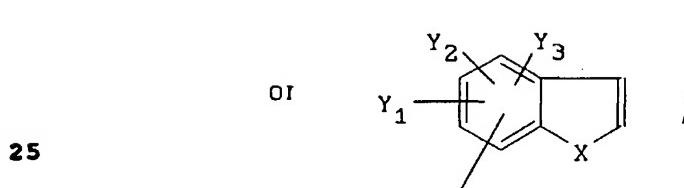
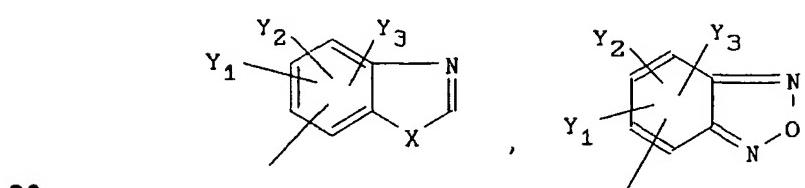
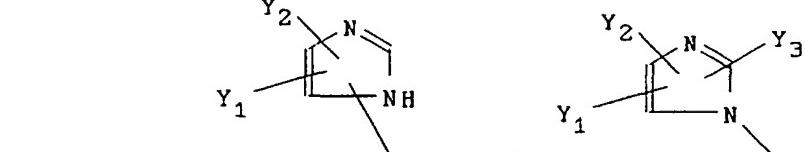
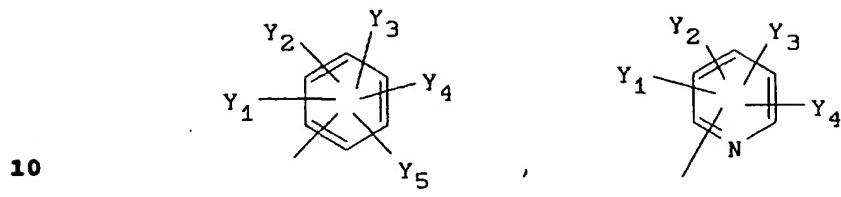
-235-

What is claimed is:

1. A compound having the structure:



5 wherein A is



wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H; straight chained or branched

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C₁-C₆ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₆ alkenyl or alkynyl; C₃-C₆ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, 5 -Br, or -I; -NO₂; -N₃; -CN; -OR₃, -OCOR₃, -COR₃, -CONHR₃, -CON(R₃)₂, or -COOR₃; or any two of Y₁, Y₂, Y₃, Y₄ and Y₅ present on adjacent carbon atoms can constitute a methylenedioxy group;

10 wherein X is S; O; or NR₃;

wherein R₁ is -H; -NO₂; -CN; straight chained or branched C₁-C₆ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₆ alkenyl or alkynyl; C₃-C₆ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂;

20 wherein R₂ is -H; straight chained or branched C₁-C₆ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₆ alkenyl or alkynyl; C₃-C₆ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃, -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃, or 25 -CH₂X(CH₂)_pNHCXR₃; or -OR₃;

30 wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;

35 wherein each R₃ is independently -H; straight chained or branched C₁-C₆ alkyl, monofluoroalkyl or

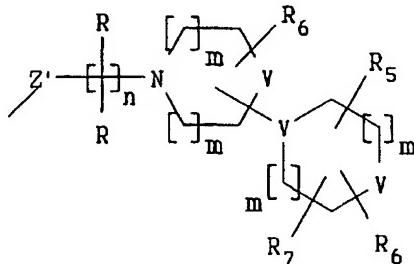
-237-

polyfluoroalkyl; straight chained or branched C₂-C₇, alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

5

wherein R₄ is

10



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wherein Z' is (CH₂)_o, CO, (CH₂)_oCO, or CO(CH₂)_o;

wherein each V is independently O; S; CH₂; CR₅R₇; C(R₇)₂; or NR₇;

20

wherein each m is independently an integer from 0 to 3; wherein o is an integer from 1 to 3;

25

wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇, alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; or -OR₃;

30

wherein R₅ and R₇ each independently may be -H; F; Cl; Br; I; -COR₃; -CO₂R₃; -CON(R₃)₂; -CN; -NO₂; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -(CH₂)_pSR₃; straight chained or branched C₁-C₇ alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl; wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with -F, -Cl, -Br, -I, -NO₂, -

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CN, -OR₃, -SR₃, C₁-C₃ alkyl, or carboxamido; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more -F, -Cl, -Br, -I, COR₃, CO₂R₃, -CON(R₃)₂, -CN, -NO₂, -N(R₃)₂, -OR₃, -SR₃, (CH₂)_nOR₃, (CH₂)_nSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl, C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and

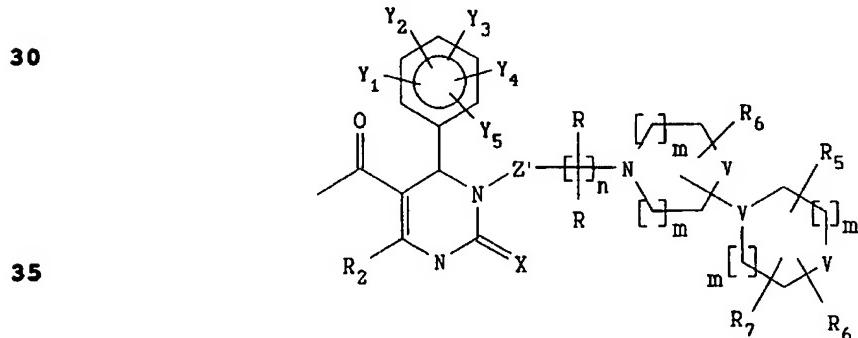
wherein each R₆ is independently -H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; or -OR₁;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound comprises the (+) enantiomer.

25 3. The compound of claim 1, wherein the compound comprises the (-) enantiomer.

4. The compound of claim 1 having the structure:

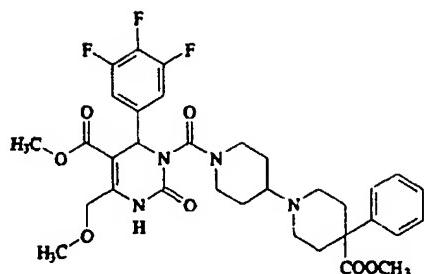


5. The compound of claim 4, wherein Z' is CO and n is 0.

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6. The compound of claim 5 having the structure:

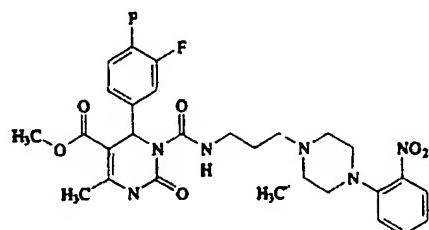
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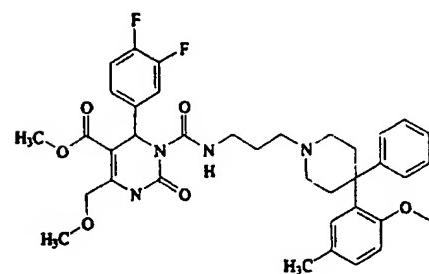
7. A compound selected from the group consisting of:

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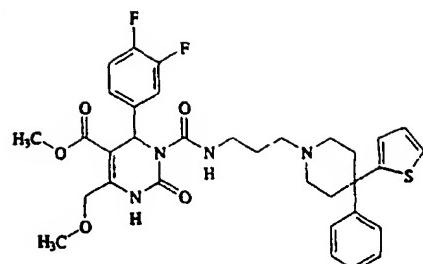


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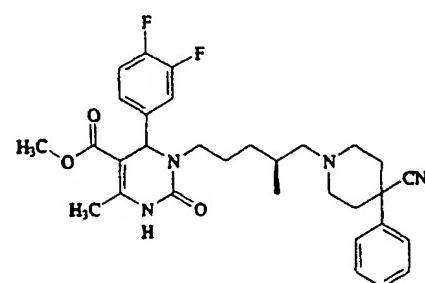
- 240 -

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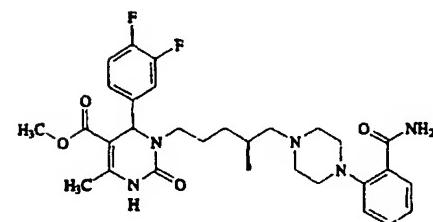
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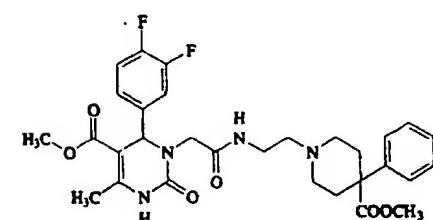


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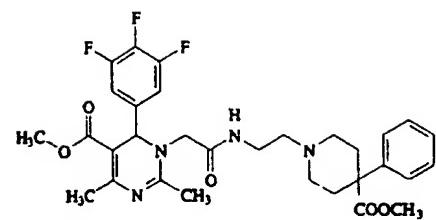
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and

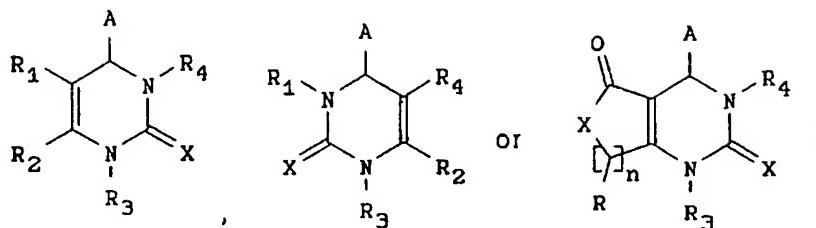
35

- 241 -



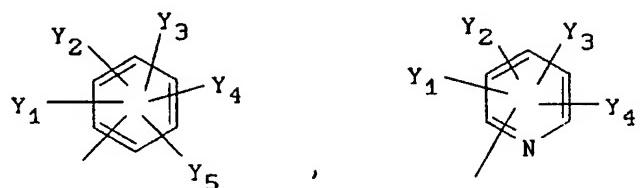
-242-

8. A compound having the structure:

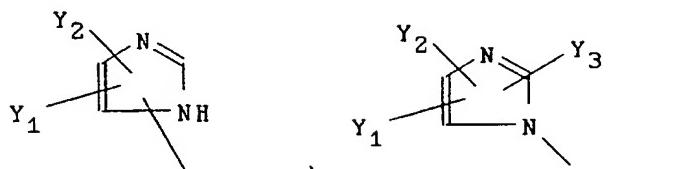


wherein A is

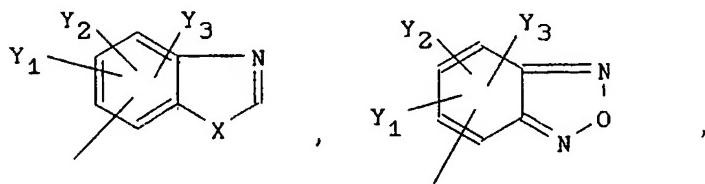
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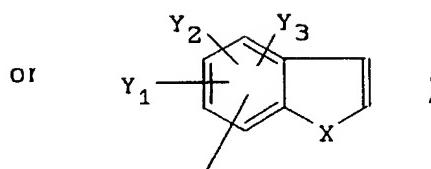
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wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl,

30

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-Br, or -I; -NO₂; -N₃; -CN; -OR₃, -OCOR₃, -COR₃, -CONHR₃, -CON(R₃)₂, or -COOR₃; or any two of Y₁, Y₂, Y₃, Y₄ and Y₅ present on adjacent carbon atoms can constitute a methylenedioxy group;

5

wherein X is S; O; or NR₃;

wherein R₁ is -H; -NO₂; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂;

15

wherein R₂ is -H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₁₀ cycloalkyl, monofluorocycloalkyl or polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃, -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃, or -CH₂X(CH₂)_pNHCXR₃; or -OR₃;

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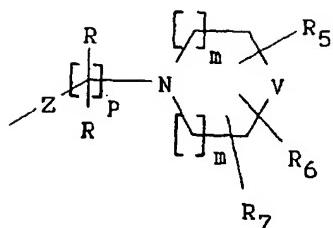
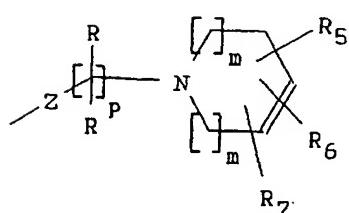
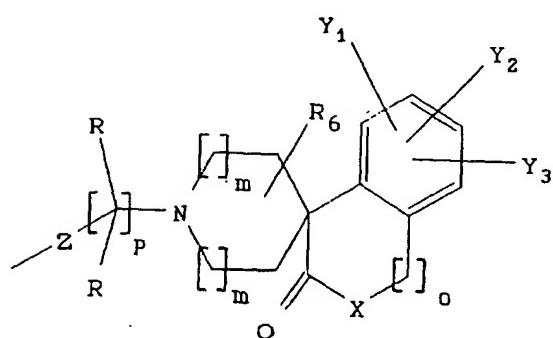
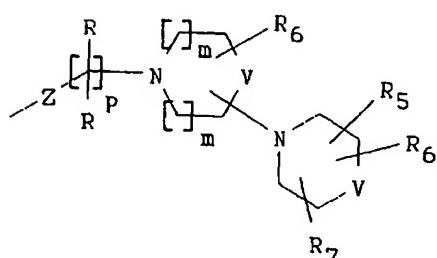
wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;

35

wherein each R₃ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

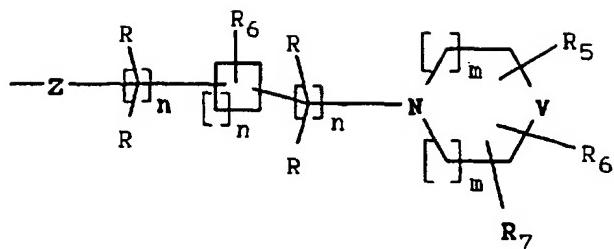
wherein R₄ is

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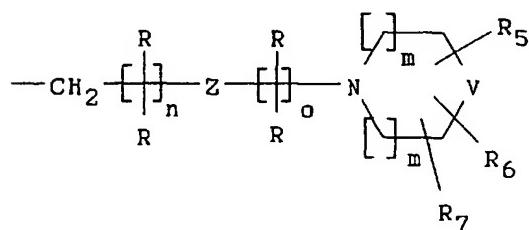
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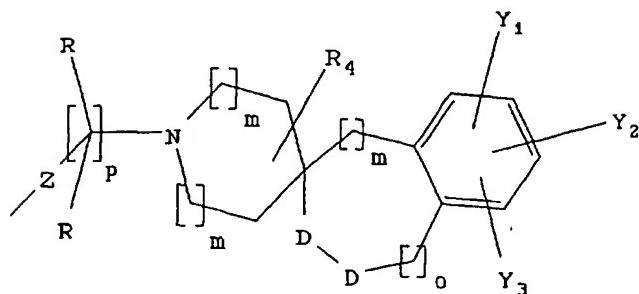
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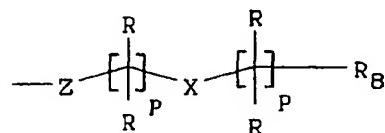


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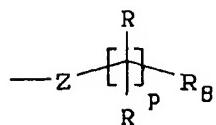
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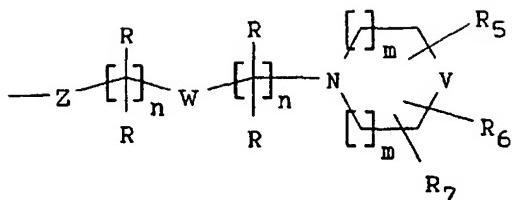


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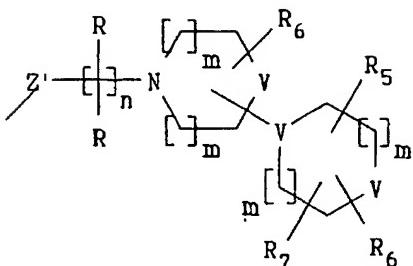
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or

10

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wherein Z is C₂-C₇ alkenyl or alkynyl; CH₂; O; CO; CO₂; CONR₃; S; SO; SO₂; or NR₃;

20

wherein Z' is (CH₂)₆; CO; (CH₂)₆CO, or CO(CH₂)₆;

wherein each D is independently CH₂; O; S; NR₃; CO; or CS;

25

wherein W is C=O; C=NOR₃; substituted or unsubstituted phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or

30

benzyimidazolyl, wherein the phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl is substituted with -H, -F, -Cl, -Br, -I, -NO₂, -CN, straight chained or branched

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C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇

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alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ monofluorocycloalkyl, C₃-C₆ polyfluorocycloalkyl, C₃-C₆ cycloalkenyl, -N(R₃)₂, -OR₃, -COR₃, -CO₂R₃, or -CON(R₃)₂;

5

wherein each V is independently O; S; CH₂; CR₅R₁; C(R₁)₂; or NR₁;

10 wherein each m is independently an integer from 0 to 3; wherein o is an integer from 1 to 3;

15 wherein each R is independently -H; -F; straight chained or branched C₁-C₆ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₆ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; or -OR₃;

20 wherein R₅ is aryl or heteroaryl substituted with one or more of F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)₆OR₃; (CH₂)₆SR₃; straight chained or branched C₁-C₆ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

25 30 wherein each R₆ is independently -H; straight chained or branched C₁-C₆ alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₆ alkenyl or alkynyl; C₃-C₆ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; or -OR₃;

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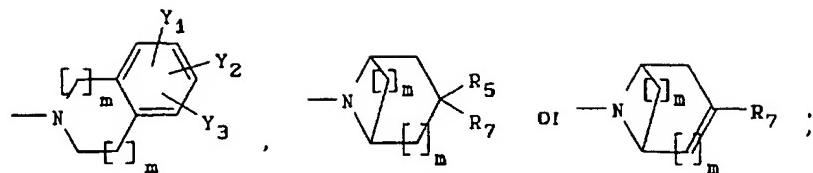
wherein R₇ is aryl or heteroaryl substituted with one or more of F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂;

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CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_nOR₃; (CH₂)_nSR₃; straight chained or branched C₁-C₆ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and

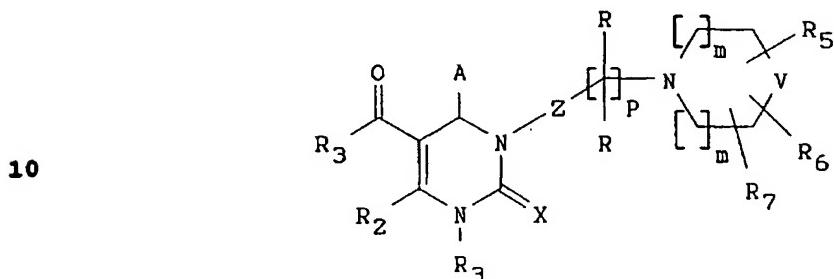
wherein R₈ is -H; substituted or unsubstituted benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolinyl, wherein the benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolinyl is substituted with -H, -F, -Cl, -Br, -I, -NO₂, -CN, straight chained or branched C₁-C₆ alkyl, straight chained or branched C₁-C₆ monofluoroalkyl, straight chained or branched C₁-C₆ polyfluoroalkyl, straight chained or branched C₂-C₆ alkenyl, straight chained or branched C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ monofluorocycloalkyl, C₃-C₆ polyfluorocycloalkyl, C₃-C₆ cycloalkenyl, -N(R₃)₂, -OR₃, -COR₃, -CO₂R₃, or -CON(R₃)₂; substituted or unsubstituted straight chained or branched C₁-C₆ alkyl, monofluoroalkyl or polyfluoroalkyl; substituted or unsubstituted straight chained or branched C₂-C₆ alkenyl or alkynyl; C₃-C₆ cycloalkyl or cycloalkenyl, wherein the alkyl, monofluoroalkyl, polyfluoroalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl is substituted with -H, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl, -N(R₃)₂, -NO₂, -CN, -CO₂R₃, -OR₃;

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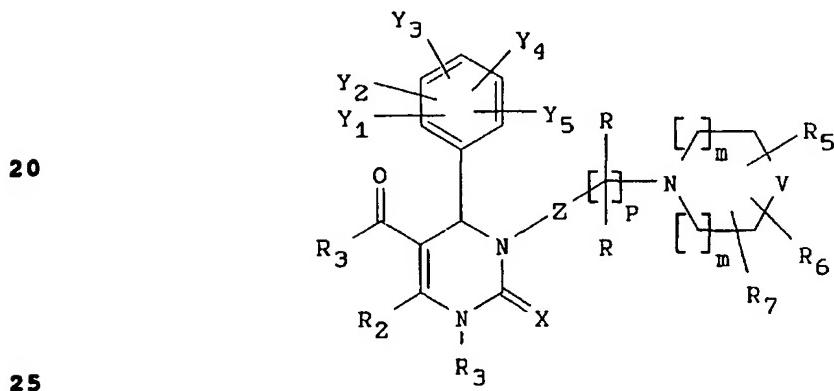


or a pharmaceutically acceptable salt thereof.

5 9. The compound of claim 8 having the structure:



15 10. The compound of claim 9 having the structure:

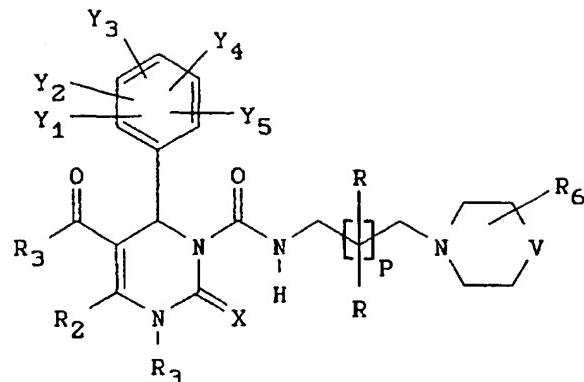


30 11. The compound of claim 10 having the structure:

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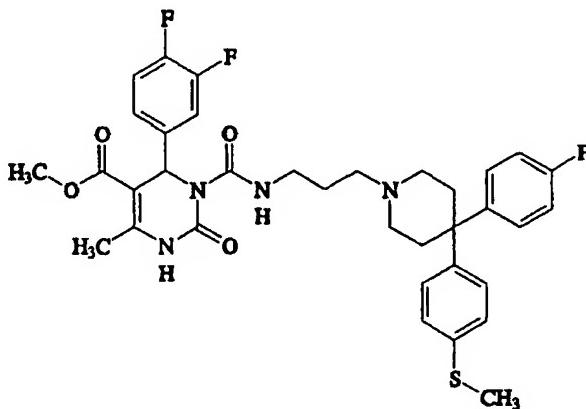
wherein V is selected from CR_5R_7 or NR_7 , and p is selected from 1-3.

15

12. The compound of claim 11, wherein the compound is selected from the group consisting of:

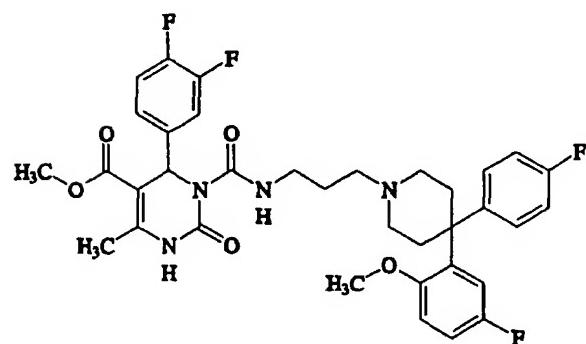
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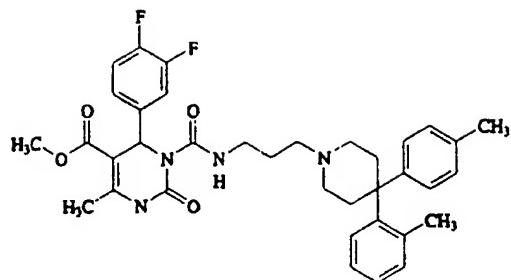
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and

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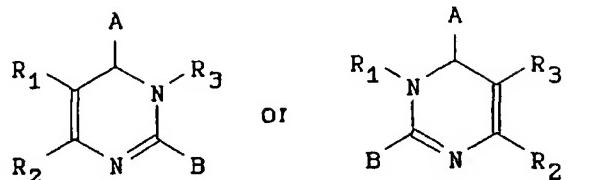
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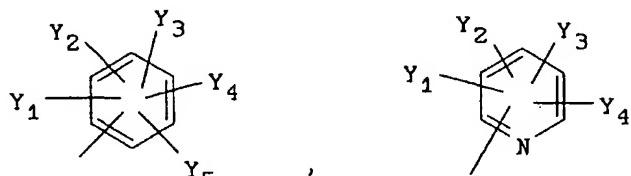
13. A compound having the structure:

5

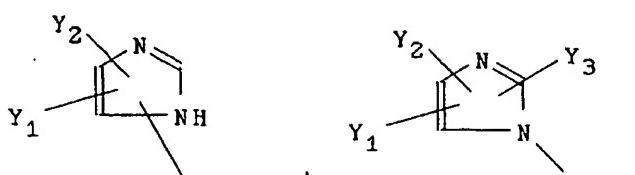


wherein A is

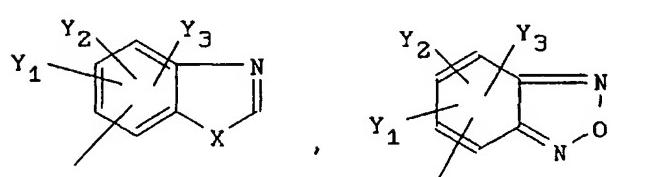
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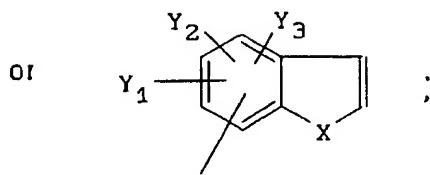
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wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,

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polyfluorocycloalkyl or cycloalkenyl; -F, -Cl,
-Br, or -I; -NO₂; -N₃; -CN; -OR₄, -OCOR₄,
-CONHR₄, -CON(R₄)₂, or -COOR₄; or any two of Y₁, Y₂,
Y₃, Y₄ and Y₅ present on adjacent carbon atoms can
5 constitute a methylenedioxy group;

wherein X is S; O; or NR₄;

10 wherein B is -H; straight chained or branched C₁-C,
alkyl, monofluoroalkyl, polyfluoroalkyl, alkoxy or
thioalkyl; straight chained or branched C₂-C,
alkenyl; -SCH₂C₆H₄OR₄; -(CH₂)_nC₆H₅; -CH₂X(CH₂)_nNHR₄;
-(CH₂)_nNHR₄; or -OR₄;

15 wherein R₁ is -H; -NO₂; -CN; straight chained or
branched C₁-C, alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C,
alkenyl or alkynyl; C₃-C, cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
20 cycloalkenyl; -N(R₄)₂; -OR₄; -(CH₂)_pOR₄; -COR₄; -
CO₂R₄; or -CON(R₄)₂;

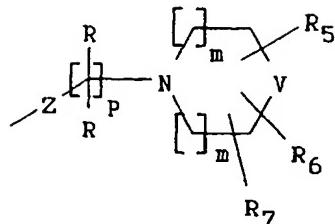
25 wherein R₂ is -H; straight chained or branched
C₁-C, alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl,
monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C₂-C, alkenyl or alkynyl; C₃-C,
cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀
30 cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-
monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-
polyfluoroalkyl; -CN; -CH₂XR₄, -CH₂X(CH₂)_pNHR₄,
-(CH₂)_nNHR₄, -CH₂X(CH₂)_pN(R₄)₂, -CH₂X(CH₂)_pN₃, or
-CH₂X(CH₂)_pNHCXR₄; or -OR₄;

35 wherein each p is independently an integer from 1
to 7; wherein each n is independently an integer
from 0 to 5;

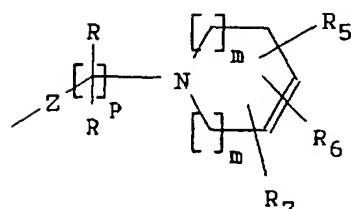
-254-

wherein R₃ is

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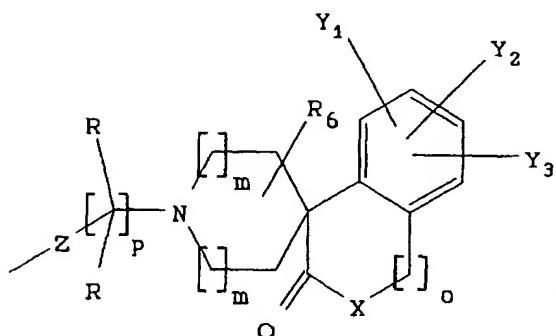


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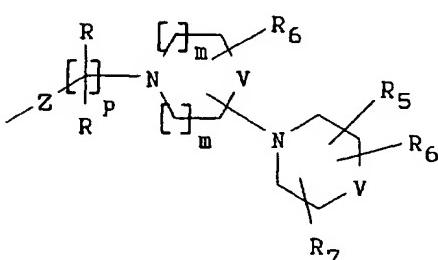
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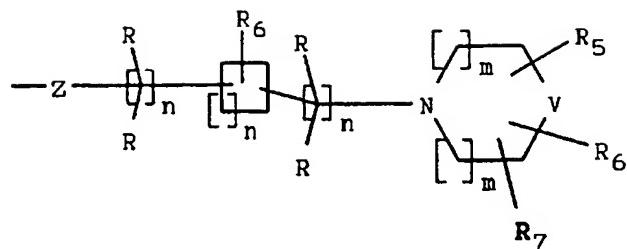
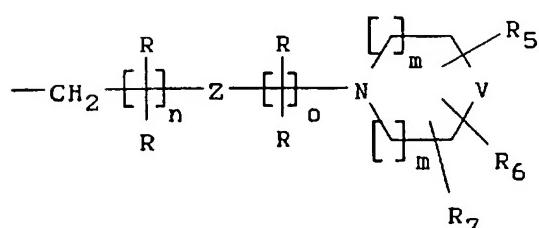
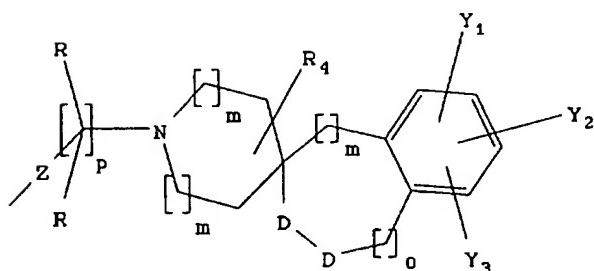
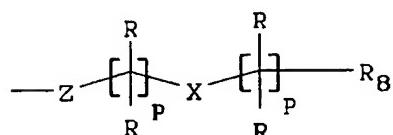
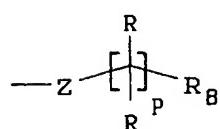


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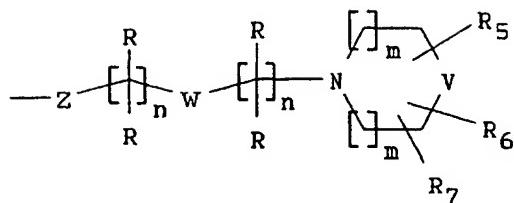


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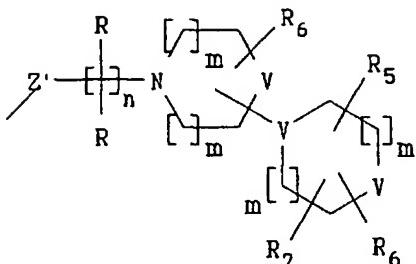
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or

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wherein Z is C₂-C₇ alkenyl or alkynyl; CH₂; O; CO; CO₂; CONR₄; S; SO; SO₂; or NR₄;

20

wherein Z' is (CH₂)₀, CO, (CH₂)₀CO, or CO(CH₂)₀;

wherein each D is independently CH₂; O; S; NR₄; CO; or CS;

25

wherein W is C=O; C=NOR₄; substituted or unsubstituted phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or

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benzyimidazolyl, wherein the phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl is substituted with -H, -F, -Cl, -Br, -I, -NO₂, -CN, straight chained or branched

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C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇

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5 alkenyl, straight chained or branched C₂-C,
alkynyl, C₃-C, cycloalkyl, C₃-C,
monofluorocycloalkyl, C₃-C, polyfluorocycloalkyl,
C₃-C, cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -CO₂R₄, or
-CON(R₄)₂;

wherein each V is independently O; S; CH₂; CR₅R₁;
C(R₇)₂; or NR₇;

10 wherein each m is independently an integer from 0
to 3; wherein o is an integer from 1 to 3;

15 wherein each R is independently -H; -F; straight
chained or branched C₁-C, alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C,
alkenyl or alkynyl; -N(R₄)₂; -NO₂; -CN; -CO₂R₄; or
-OR₄;

20 wherein each R₄ is independently -H; straight
chained or branched C₁-C, alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C,
alkenyl or alkynyl; C₃-C, cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

25 wherein R₅ is aryl or heteroaryl substituted with
one or more of F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂;
CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_oOR₃; (CH₂)_oSR₃;
30 straight chained or branched C₁-C, alkyl,
monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or branched
C₂-C, alkenyl, C₂-C, alkynyl, C₃-C, cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

35 wherein each R₆ is independently -H; straight
chained or branched C₁-C, alkyl, hydroxyalkyl,

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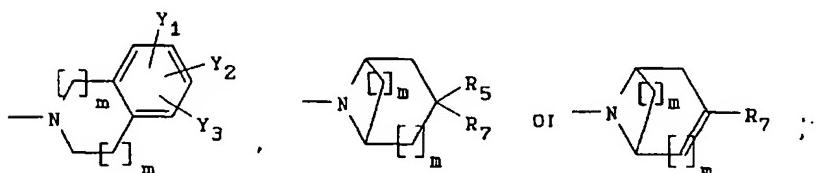
aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C, alkenyl or alkynyl; C₃-C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; or -OR₄;

wherein R, is aryl or heteroaryl substituted with one or more of F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_nOR₃; (CH₂)_nSR₃; straight chained or branched C₁-C, alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C, alkenyl, C₂-C, alkynyl, C₃-C, cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and

wherein R₈ is -H; substituted or unsubstituted benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolinyl, wherein the benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolinyl is substituted with -H, -F, -Cl, -Br, -I, -NO₂, -CN, straight chained or branched C₁-C, alkyl, straight chained or branched C₁-C, monofluoroalkyl, straight chained or branched C₁-C, polyfluoroalkyl, straight chained or branched C₂-C, alkenyl, straight chained or branched C₂-C, alkynyl, C₃-C, cycloalkyl, C₃-C, monofluorocycloalkyl, C₃-C, polyfluorocycloalkyl, C₃-C, cycloalkenyl, -N(R₄)₂, -OR₄, -COR₄, -CO₂R₄, or -CON(R₄)₂; substituted or unsubstituted straight chained or branched C₁-C, alkyl, monofluoroalkyl or polyfluoroalkyl; substituted or unsubstituted straight chained or branched C₂-C, alkenyl or

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5 alkynyl; C₃-C₆ cycloalkyl or cycloalkenyl, wherein the alkyl, monofluoroalkyl, polyfluoroalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl is substituted with -H, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrryl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl, -N(R₄)₂, -NO₂, -CN, -CO₂R₄, -OR₄;



or a pharmaceutically acceptable salt thereof.

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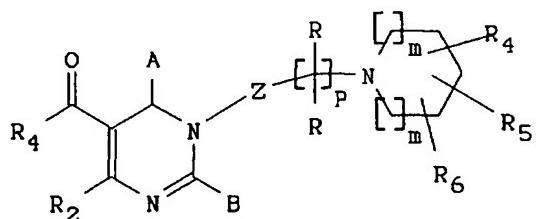
14. The compound of claim 13, wherein the compound comprises the (-) enantiomer.

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15. The compound of claim 13, wherein the compound comprises the (+) enantiomer.

16. The compound of claim 13 having the structure:

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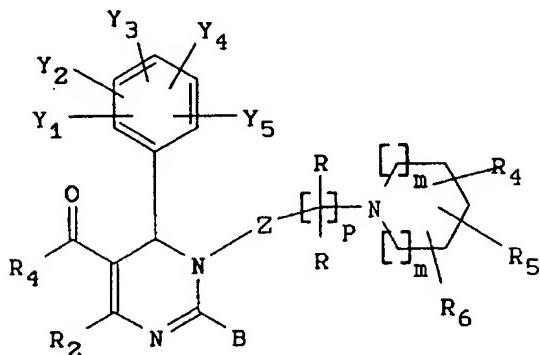
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17. The compound of claim 16 having the structure:

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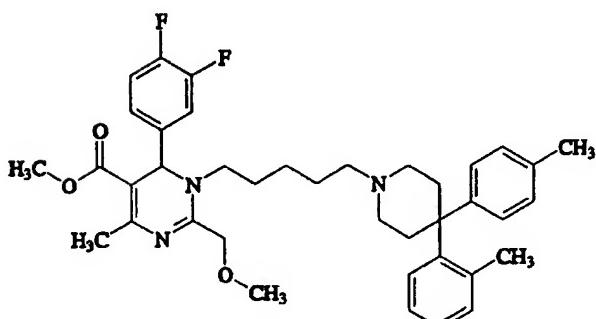
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25

and

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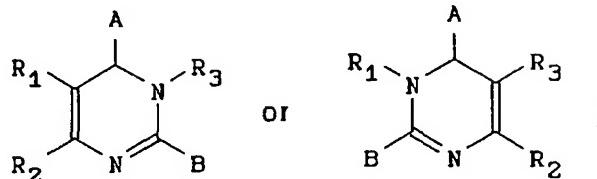
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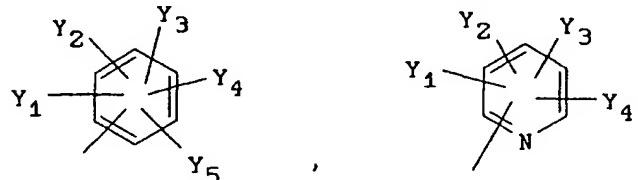
19. A compound having the structure:

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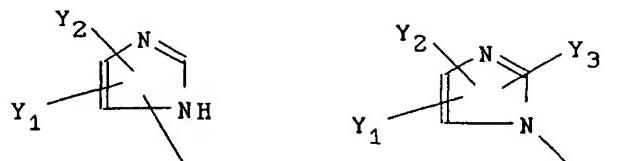


wherein A is

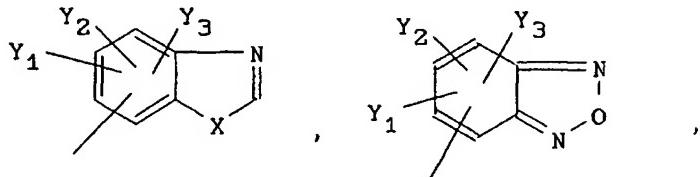
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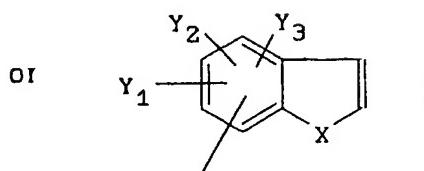
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wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₄, -OCOR₄, -COR₄, -CONHR₄, -CON(R₄)₂, or -COOR₄; or any two of Y₁, Y₂, Y₃, Y₄ and Y₅ present on adjacent carbon atoms can

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constitute a methylenedioxy group;

wherein X is S; O; or NR₄;

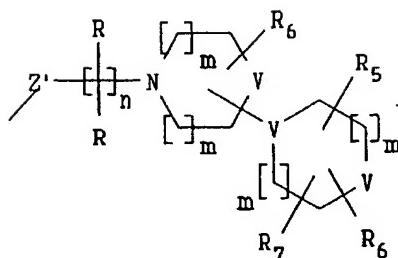
5 wherein B is -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, alkoxy or thioalkyl; straight chained or branched C₂-C₇ alkenyl; -SCH₂C₆H₄OR₄; -(CH₂)_nC₆H₅; -CH₂X(CH₂)_nNHR₄; -(CH₂)_nNHR₄; or -OR₄;

10 wherein R₁ is -H; -NO₂; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₄)₂; -OR₄; -(CH₂)_pOR₄; -COR₄; -CO₂R₄; or -CON(R₄)₂;

20 wherein R₂ is -H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₁₀ cycloalkyl, monofluorocycloalkyl or cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₄, -CH₂X(CH₂)_pNHR₄, -(CH₂)_nNHR₄, -CH₂X(CH₂)_pN(R₄)₂, -CH₂X(CH₂)_pN₃, or -CH₂X(CH₂)_pNHCXR₄; or -OR₄;

25 wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;
30 wherein R₃ is
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wherein Z' is $(CH_2)_o$, CO , $(CH_2)_oCO$, or $CO(CH_2)_o$;

10 wherein each V is independently O ; S ; CH_2 ; CR_6R_7 ; $C(R_7)_2$; or NR_7 ;

15 wherein each m is independently an integer from 0 to 3; wherein o is an integer from 1 to 3;

20 wherein each R is independently $-H$; $-F$; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; $-N(R_4)_2$; $-NO_2$; $-CN$; $-CO_2R_4$; or $-OR_4$;

25 wherein each R_4 is independently $-H$; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

30 wherein R_5 and R_7 each independently may be $-H$; F ; Cl ; Br ; I ; $-COR_3$; $-CO_2R_3$; $-CON(R_3)_2$; $-CN$; $-NO_2$; $-N(R_3)_2$; $-OR_3$; $-SR_3$; $-(CH_2)_pOR_3$; $-(CH_2)_pSR_3$; straight chained or branched C_1-C_7 alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl or cycloalkenyl; wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl

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may be substituted with -F, -Cl, -Br, -I, -NO₂, -CN, -OR₃, -SR₃, C₁-C₆ alkyl, or carboxamido; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more -F, -Cl, -Br,
5 -I, COR₃, CO₂R₃, -CON(R₃)₂, -CN, -NO₂, -N(R₃)₂, -OR₃, -SR₃, (CH₂)_nOR₃, (CH₂)_nSR₃; straight chained or branched C₁-C₆ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and

10
15 wherein each R₆ is independently -H; straight chained or branched C₁-C₆ alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₆ alkenyl or alkynyl; C₃-C₆ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; or -OR₄;

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or a pharmaceutically acceptable salt thereof.

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20. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.
21. The pharmaceutical composition of claim 20 wherein the amount of the compound is an amount from about 0.01 mg to about 500 mg.
22. The pharmaceutical composition of claim 21 wherein the amount of the compound is from about 0.1 mg to about 60 mg.
23. The pharmaceutical composition of claim 22 wherein the amount of the compound is from about 1 mg to about 20 mg.

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24. The pharmaceutical composition of claim 20, wherein the carrier is a liquid and the composition is a solution.
- 5 25. The pharmaceutical composition of claim 20, wherein the carrier is a solid and the composition is a tablet.
- 10 26. The pharmaceutical composition of claim 20, wherein the carrier is a gel and the composition is a suppository.
- 15 27. The pharmaceutical composition of claim 20, wherein the compound additionally does not cause a fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia.
- 20 28. A method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim 1 effective to treat benign prostatic hyperplasia.
- 25 29. A method of claim 28, wherein the compound additionally does not cause a fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia.
- 30 30. The method of claim 29, wherein the compound effects treatment of benign prostatic hyperplasia by relaxing lower urinary tract tissue.
- 35 31. The method of claim 30, wherein lower urinary tract tissue is prostatic smooth muscle.
32. A method of treating a subject suffering from high intraocular pressure which comprises administering to the subject an amount of the compound of claim 1 effective to lower intraocular pressure.

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33. A method of treating a subject suffering from a disorder associated with high cholesterol which comprises administering to the subject an amount of the compound of claim 1 effective to inhibit cholesterol synthesis.
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34. A method of treating a disease which is susceptible to treatment by antagonism of the α_{1A} receptor which comprises administering to the subject an amount of the compound of claim 1 effective to treat the disease.
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35. A method of treating a subject suffering from impotency which comprises administering to the subject an amount of the compound of claim 1 effective to treat impotency.
15
36. A method of treating a subject suffering from sympathetically mediated pain which comprises administering to the subject an amount of the compound of claim 1 effective to treat sympathetically mediated pain.
20
37. A method of treating a subject suffering from cardiac arrhythmia which comprises administering to the subject an amount of the compound of claim 1 effective to treat cardiac arrhythmia.
25
38. A method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim 1 effective to treat benign prostatic hyperplasia.
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39. The method of claim 38, wherein the compound effects treatment of benign prostatic hyperplasia by relaxing lower urinary tract tissue.
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40. The method of claim 39, wherein lower urinary

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tract tissue is prostatic smooth muscle.

41. A method of treating a subject suffering from benign prostatic hyperplasia which comprises
5 administering to the subject an amount of the compound of claim 1 in combination with a 5 alpha-reductase inhibitor effective to treat benign prostatic hyperplasia.
- 10 42. The method of claim 41, wherein the 5-alpha reductase inhibitor is finasteride.
- 15 43. A method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject an amount of the compound of claim 1 in combination with a 5 alpha-reductase inhibitor effective to treat benign prostatic hyperplasia.
- 20 44. The method of claim 43, wherein the 5-alpha reductase inhibitor is finasteride.
- 25 45. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 in combination with a therapeutically effective amount of finasteride and a pharmaceutically acceptable carrier.
- 30 46. The pharmaceutical composition of claim 45 wherein the compound is present in an amount from about 0.01 mg to about 500 mg and the therapeutically effective amount of the finasteride is about 5 mg.
- 35 47. The pharmaceutical composition of claim 46 wherein the compound is present in an amount from about 0.1 mg to about 60 mg and the therapeutically effective amount of finasteride is about 5 mg.
48. The pharmaceutical composition of claim 47 wherein

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the compound is present in an amount from about 1 mg to about 20 mg and the therapeutically effective amount of finasteride is about 5 mg.

- 5 49. A method of relaxing lower urinary tract tissue which comprises contacting the lower urinary tract tissue with an amount of the compound of claim 1 effective to relax lower urinary tract tissue.
- 10 50. The method of claim 49, wherein the lower urinary tract tissue is prostatic smooth muscle.
- 15 51. A method of relaxing lower urinary tract tissue in a subject which comprises administering to the subject an amount of the compound of claim 1 effective to relax lower urinary tract tissue.
52. The method of claim 51, wherein the lower urinary tract tissue is prostatic smooth muscle.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/08335

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/505; C07D 239/36

US CL :514/274; 544/243, 315, 316

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/274; 544/243, 315, 316

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,855,301 A (ATWAL et al) 08 August 1989, col. 1-8, entire disclosure.	1-7, 20-31 and 45-48
X	US 5,202,330 A (ATWAL et al) 13 April 1993,col. 3, lines 5-65, formula (I).	1-7, 20-31 and 45-48

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

21 AUGUST 1997

Date of mailing of the international search report

11 SEP 1997

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08335

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-7, 20-31 and 45-48

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

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